

THE AMERICAN HEART JOURNAL



©Am. Ht. Assn.

A JOURNAL FOR THE STUDY OF THE CIRCULATION

PUBLISHED MONTHLY

UNDER THE EDITORIAL DIRECTION OF

THE AMERICAN HEART ASSOCIATION

Fred M. Smith - - - - - Editor-in-Chief

Associate Editors

Hugh McCulloch

Irving S. Wright

Horace M. Korns

Editorial Board

EDGAR V. ALLEN
CLAUDE S. BECK
HARRY GOLDBLATT
GEORGE HERRMANN
WILLIAM J. KERR
ROBERT L. LEVY
H. M. MARVIN

JONATHAN C. MEAKINS
ROY W. SCOTT
ISAAC STARR
J. MURRAY STEELE
PAUL D. WHITE
FRANK N. WILSON
CHARLES C. WOLFERTH

VOLUME 17
JANUARY—JUNE, 1939

ST. LOUIS
THE C. V. MOSBY COMPAN
1939

COPYRIGHT, 1939, BY THE C. V. MOSBY COMPANY

(All rights reserved)

Printed in the United States of America

*Press of
The C. V. Mosby Company
St. Louis*

The American Heart Journal

VOL. 17

JANUARY, 1939

No. 1

Original Communications

THE CYANOSIS IN MITRAL STENOSIS

PEDRO COSSIO, M.D., AND ISAAC BERCONSKY, M.D.

BUENOS AIRES, ARGENTINE

IN THE beginning of the last century Corvisart¹ pointed out as a sign of heart affection a particular alteration of the face, characterized by a "violet coloration." A few years afterward, Bertin² expressed in a more precise manner the significance of this facial characteristic noted by Corvisart, referring to it as a sign of "induration and constriction of the heart valves." Subsequently, Bouillaud,³ considering endocarditis and especially the symptoms and the diagnosis of the organic lesions of the valves with stenosis of the heart openings, referred to the facial changes in heart disease and reported a case of mitral stenosis in which there was this particular cyanotic tincture of the face.

Later, Huchard⁴ differentiated, among the diverse clinical pictures of mitral stenosis, the cyanotic form that is characterized by a pronounced violaceous coloration of the face and lips which appears with the least effort and without considerable manifestations of cardiac insufficiency.

Barié,⁵ considering the different types of facies in the valvular cardiopathies, differentiated the "aortic facies" of dull white color similar to that seen in anemia and the mitral facies of a violaceous coloration, the lips and wings of the nose being livid-cyanotic and the cheek bones crossed by bluish venules. On this cyanotic ground one can perceive a light subicteric tint that is more pronounced in the conjunctivae.

This particular cyanotic coloration which represents and distinguishes mitral stenosis has been explained by Walshe⁶ as a result of interference with the oxygenation of the blood in the lung, brought on by the circulatory hindrance arising from a mitral lesion which obstructs the outflow of blood from the lung. Dautrebande, Fetter, and Meakins,⁷ on the other hand, on the basis of a study of blood gases in four patients with mitral stenosis without clinical signs of lung congestion, have claimed that the saturation of oxygen of the arterial blood was normal, but, as soon as the

*From the Department of Heart Diseases, Instituto de Semiologia. Director: Professor T. Padilla, Hospital de Clínicas. Facultad de Medicina.

Received for publication Feb 20, 1938.

TABLE
MEASUREMENTS MADE ON 22

CASE	DEGREE OF CYANOSIS	CIRCULATION TIME (SECONDS) *	VENOUS PRESSURE (MM. H ₂ O)	VITAL CAPACITY (LITERS)	ALVEOLAR AIR				ARTERIAL BLOOD GASES CONTENT (VOL. PER CENT)		VENOUS BLOOD GASES CONTENT (VOL. PER CENT)		ARTERIOVENOUS OXYGEN DIFFERENCE (VOL. PER CENT)
					OXYGEN		CARBON DIOXIDE		OXYGEN	CARBON DIOXIDE	OXYGEN	CARBON DIOXIDE	
					PER CENT	MM. Hg	PER CENT	MM. Hg					
1	+++	S = 50 R = 60	---	---	----	-----	---	----	14.7	39.7	6.8	43.4	7.9
	+++	---	---	1.40	15.87	113.91	4.65	33.37	16.9	51.1	9.9	56.9	7.0
2	++	R = 45	170	1.30	14.28	102.53	4.49	32.23	21.4	42.3	11.2	50.6	10.2
	+	S = 35 R = 40	164	2.05	13.07	93.38	4.75	33.93	24.0	40.5	10.9	51.0	13.1
3	+	---	---	2.00	15.22	108.06	5.27	37.41	23.6	45.0	8.0	55.0	15.6
	+++	S = 45 R = 48	250	1.50	15.74	112.38	4.47	31.91	23.3	40.1	8.0	53.1	15.3
	+	S = 35 R = 38	250	2.00	15.62	112.30	5.00	35.95	23.2	39.1	8.2	52.3	15.0
4	+	S = 50 R = 42	220	2.90	17.90	128.34	2.64	18.92	23.3	31.6	8.7	41.8	14.6
	0	---	140	3.10	15.11	107.43	4.71	33.48	19.7	40.6	13.4	53.2	6.3
	++	32(D)	240	---	----	-----	---	----	23.18	39.78	9.62	54.57	13.5
5	+	S = 24 R = 28	---	3.25	14.00	99.82	6.03	42.99	22.93	49.72	13.59	53.66	9.3
	+	S = 17 R = 25	238	---	----	-----	---	----	23.90	47.20	12.0	58.0	11.9
6	+	S = 30 R = 35	170	1.70	14.32	101.95	5.10	36.31	18.7	47.0	9.2	52.5	9.5
	0	S = 24 R = 26	117	2.30	14.17	101.03	5.20	37.07	19.6	43.7	10.8	51.5	8.8
7	+	S = 20 R = 35	183	2.20	15.86	113.24	4.65	33.20	19.0	38.0	6.0	48.0	13.0
8	++	S = 28 R = 32	205	2.10	16.05	114.75	3.61	25.81	16.9	36.0	7.0	48.0	9.9
9	+	R = 23	---	3.00	13.65	97.46	5.19	37.05	19.5	39.7	12.1	48.3	7.4
10	+	S = 24 R = 27	250	3.90	14.30	101.15	5.79	40.37	23.3	37.5	8.5	53.7	14.8
11	+	---	---	2.80	16.10	113.92	3.48	24.62	20.5	28.4	8.0	42.3	12.5
12	0	R = 35	205	2.30	15.72	111.76	4.14	29.43	19.1	39.0	11.9	45.0	7.2
13	+	S = 23 R = 28	---	2.45	14.04	99.68	4.79	34.00	16.1	51.9	9.0	57.4	7.1
14	++	---	250	2.20	15.58	112.33	3.73	26.89	26.18	42.9	----	---	---
15	0	---	115	3.50	13.14	94.08	6.06	42.38	17.5	53.0	8.45	58.0	9.05
16	+	S = 23 R = 25	85?	2.40	14.46	102.52	5.61	39.77	27.50	48.21	10.25	60.39	17.25
	++	---	95?	1.90	14.86	106.10	4.75	33.91	17.0	42.4	7.7	51.4	9.3
17	+	---	230	2.95	----	-----	4.26	30.33	24.6	33.8	9.3	50.0	15.3
	++	S = 35 R = 40	230	2.60	15.62	111.21	4.66	32.87	20.7	43.1	6.7	52.0	14.0
18	+	32(D)	240	---	----	-----	---	----	22.15	39.58	15.0	43.64	7.15
19	+	12(D)	122	---	----	-----	---	----	23.35	35.43	14.28	41.60	9.07
20	+	---	---	---	----	-----	---	----	19.11	45.18	8.95	51.13	10.55
21	++	25(D)	250	---	----	-----	---	----	21.75	45.98	11.16	50.43	10.59
22	+	---	---	---	----	-----	---	----	19.06	40.22	14.54	41.92	4.52

*S = taste and R = redness (histamine method); D = taste (decholin method).

SUBJECTS WITH MITRAL STENOSIS

OXYGEN CAPACITY (VOL. PER CENT)	OXYGEN UNSATURA- TION (VOL. PER CENT)		OXYGEN SATURATION (PER CENT)		CAPILLARY OXYGEN UNSATURATION (VOL. PER CENT)	REDUCED HEMOGLOBIN- CAPILLARY BLOOD (GM. PER CENT)	FUNCTIONAL CAPACITY	CLINICAL REMARKS
	ARTERIAL BLOOD	VENOUS BLOOD	ARTERIAL BLOOD	VENOUS BLOOD				
21.8	7.1	15.0	67.5	31.2	11.05	8.2	3	Mitral stenosis, auricular fibrillation. Congestive heart failure, pulmonary congestion
21.8	4.9	11.9	77.6	45.5	8.4	6.2	2 b	Improvement
27.1	5.7	15.9	79.0	41.4	10.8	8.0	2 b	Mitral stenosis, auricular fibrillation, pulmonary congestion
25.5	1.5	14.6	94.2	43.0	8.0	5.9	2 a	Improvement
24.8	1.2	16.8	96.0	33.0	9.0	6.7	1	Mitral stenosis, auricular fibrillation
24.8	1.5	16.8	94.0	34.3	9.15	6.8	2 b	Congestive heart failure
24.8	1.6	16.6	93.6	33.1	9.10	6.7	1	Definite improvement
24.0	0.70	15.3	97.1	36.3	8.0	5.9	3	Mitral stenosis, auricular fibrillation, congestive heart failure
20.7	1.0	7.3	95.0	64.7	4.15	3.0	1	Definite improvement
24.05	0.87	14.43	96.3	40.0	7.65	5.7	2 b	Congestive heart failure
26.48	4.55	12.89	86.6	51.4	8.72	6.5	2 a	Mitral stenosis, paroxysmal auricular fibrillation
26.30	2.40	14.90	91.0	46.0	8.65	6.4	1	Definite improvement
20.2	1.5	11.0	92.6	45.6	6.25	4.6	2 b	Mitral stenosis, auricular fibrillation
19.8	0.20	9.0	99.0	54.6	4.60	3.4	1	Definite improvement
20.0	1.0	14.0	95.0	30.0	7.5	5.5	1	Mitral stenosis, auricular fibrillation
20.0	3.1	13.0	84.5	35.0	8.05	6.0	2 b	Mitral stenosis, auricular flutter, pul- monary congestion
25.2	5.7	13.1	77.4	48.1	9.40	7.0	1	Mitral stenosis
28.0	4.7	19.5	83.3	30.4	12.10	9.0	1	Mitral stenosis, auricular fibrillation
22.4	1.9	14.4	91.8	35.8	8.15	6.0	2 b	Mitral stenosis, auricular fibrillation, adherent pericarditis
20.8	1.7	8.9	92.0	58.0	5.30	3.9	2 b	Mitral stenosis, aortic insufficiency
20.9	4.8	11.9	77.1	43.1	8.35	6.2	1	Mitral stenosis, auricular fibrillation
32.61	6.4	----	80.29	---	---	--	2 b	Mitral stenosis
18.8	1.3	10.3	93.6	45.0	5.80	4.3	1	Mitral stenosis, aortic stenosis
29.14	1.6	18.8	94.4	35.2	10.2	7.6	2 a	Mitral stenosis, aortic valve disease
24.5	7.5	16.8	69.4	31.5	12.1	9.0	3	Congestive heart failure, pulmonary congestion
27.7	3.1	18.4	89.0	34.0	10.7	7.9	1	Mitral stenosis, aortic valve disease, auricular fibrillation
27.7	7.0	21.0	74.8	24.2	14.0	10.4	3	Congestive heart failure, pulmonary congestion
22.56	0.41	7.56	98.18	66.48	3.98	2.9	1	Mitral stenosis, auricular fibrillation, "facies mitral"
23.77	0.42	9.49	98.2	60.0	4.95	3.6	2 a	Mitral stenosis, hyperthyroidism, auri- cular fibrillation, "facies mitral"
19.50	0.39	10.55	98.0	45.89	5.47	4.0	1	Mitral stenosis, "facies mitral"
22.52	0.77	11.36	96.5	49.55	6.06	4.5	1	Mitral stenosis, auricular fibrillation
19.66	0.60	5.12	96.9	73.90	2.86	2.1	2 a	Mitral stenosis, aortic insufficiency, "facies mitral"

venous pressure became increased and signs of viscerai congestion appeared, arterial oxygen unsaturation set in. As the cyanosis of mitral stenosis is not well understood, it seems worth while to report studies on a group of patients.

METHOD AND MATERIAL

Each patient was investigated under basal conditions. The following measurements were made: The speed of the blood flow by the histamines or by the decholin method;⁹ the venous pressure by the direct method with a water manometer; the vital capacity of the lungs with the Verdin spirometer; the alveolar oxygen and carbon dioxide by the Haldane and Priestley method;¹⁰ the oxygen and carbon dioxide content of the arterial and venous blood by the Van Slyke and Stadie method;¹¹ the arteriovenous oxygen difference; oxygen capacity of the blood; saturation percentage of the arterial and venous blood; reduced hemoglobin in capillary blood by the Lundsgaard and Van Slyke procedure;¹² estimation of the degree of cyanosis according to the method already described;¹³ and functional capacity according to the point of view of the American Heart Association¹⁴ (Table I).

Twenty-two patients were investigated. The distribution of the cases was as follows: Mitral stenosis with sinus rhythm, 3; mitral stenosis with auricular fibrillation, 14; mitral stenosis with aortic regurgitation and sinus rhythm, 4; mitral stenosis with aortic regurgitation and auricular fibrillation, 1. The clinical diagnosis as well as the state of the lungs was established by clinical, radiographic and electrocardiographic examinations. In 6 cases the diagnosis was confirmed by necropsy (Cases 1, 2, 4, 11, 16 and 17).

COMMENTS

Among the 22 patients studied only 2 (Cases 12 and 15) had no cyanosis, while the other 20 presented varying degrees of cyanosis. In the 2 patients without cyanosis mitral stenosis coexisted with aortic regurgitation, although there were patients with cyanosis with this same combination of valvular lesions (Cases 16 and 17, Table II).

Of the 20 patients with cyanosis (Table I), the reduced hemoglobin in the capillary blood was at least 4.5 gm. (which is the minimal quantity that is necessary for the appearance of the cyanotic coloration) in 15 (Cases 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 16, 17 and 21). In these 15 patients with cyanosis and increase of the reduced hemoglobin, the cause of the cyanosis varied. In 6 cases (Cases 3, 4, 6, 7, 11 and 21) it was peripheral cyanosis; that is to say, there was an increased delivery of oxygen at the capillaries. In the other 9 (Cases 1, 2, 5, 8, 9, 10, 13, 16 and 17) it was of the mixed variety, due to increased delivery of oxygen, on the one hand, and to increased arterial unsaturation, on the other. The latter was never found to be the only cause of cyanosis, that is to say, cyanosis was never exclusively of the central variety. In some of the patients with mixed cyanosis (Cases 2, 5, 16, and 17), when the cardiac failure diminished, the arterial unsaturation lessened or even disappeared (Cases 2 and 5), while with an increase of cardiac failure there was also an increase of the arterial unsaturation (Cases 16 and 17, Table II).

The greater peripheral utilization of oxygen, the cause of the cyanosis in the patients above mentioned, was due to circulatory stasis, which was partly a consequence of the existing cardiac failure (back pressure) and partly due to the venous hindrance in the region of the vena cava superior. This resulted from mechanical disturbances brought about by the enlargement of the left auricle and rotation of the heart due to stenosis of the mitral valve.

TABLE II

ARTERIAL OXYGEN SATURATION, CAPILLARY HEMOGLOBIN, AND DEGREE OF CYANOSIS IN 4 SUBJECTS WITH MITRAL STENOSIS WITH VARYING DEGREES OF FUNCTIONAL CAPACITY

CASES	DEGREE OF CYANOSIS	FUNCTIONAL CAPACITY	ARTERIAL OXYGEN SATURATION (PER CENT)	REDUCED HEMOGLOBIN IN CAPILLARY BLOOD (GM. PER CENT)	CLINICAL REMARKS
2	++	2b	79.0	8.0	Pulmonary congestion
	+	2a	94.0	5.9	-----
5	+	2a	86.6	6.5	-----
	+	1	91.0	6.4	-----
16	+	2a	94.4	7.6	-----
	++	3	69.4	9.0	Pulmonary congestion
17	+	1	89.0	7.9	-----
	++	3	74.8	10.4	Pulmonary congestion

This mechanical disturbance at the level of the vena cava superior in mitral stenosis has been observed by us over and over again when we performed catheterization of the right auricle, introducing a catheter through a vein of the fold of the elbow.¹⁵ In normal people, as well as in patients with arterial hypertension or aortic regurgitation with varying degrees of heart failure, the catheter reached the right auricle without

TABLE III

VENOUS PRESSURE AND ARTERIOVENOUS OXYGEN DIFFERENCE IN 7 SUBJECTS WITH MITRAL STENOSIS WITHOUT HEART FAILURE

CASE	FUNCTIONAL CAPACITY	VENOUS PRESSURE (MM. H ₂ O)	ARTERIOVENOUS OXYGEN DIFFERENCE (VOL. PER CENT)
3	1	250	15.0
5	1	238	11.9
7	1	183	13.0
10	1	250	14.8
17	1	230	15.3
18	1	240	7.15
21	1	250	10.59

meeting any obstacle, taking the following course: vena axillaris and vena subclavia, the innominate vein and vena cava superior (Fig. 1). In the patients with mitral stenosis and enlargement of the left auricle, on the other hand, it was the rule that when the catheter reached the vena cava superior it met with an obstacle that prevented its arrival at the

right auricle; thus in more than one instance, in trying to overcome the obstacle by force and pushing the catheter with maintained pressure, its point turned around and entered the internal jugular vein (Fig. 2). The presence of this obstacle at the level of the vena cava superior may account satisfactorily for the increase of the venous pressure at the level of the elbow fold and the lack of correlation between pressure in the external jugular vein and the degree of heart failure in mitral stenosis, as was seen in the observations in Table III.

Increase of the arterial unsaturation as the cause of the central cyanosis in several of the cases studied cannot be attributed to a venous-

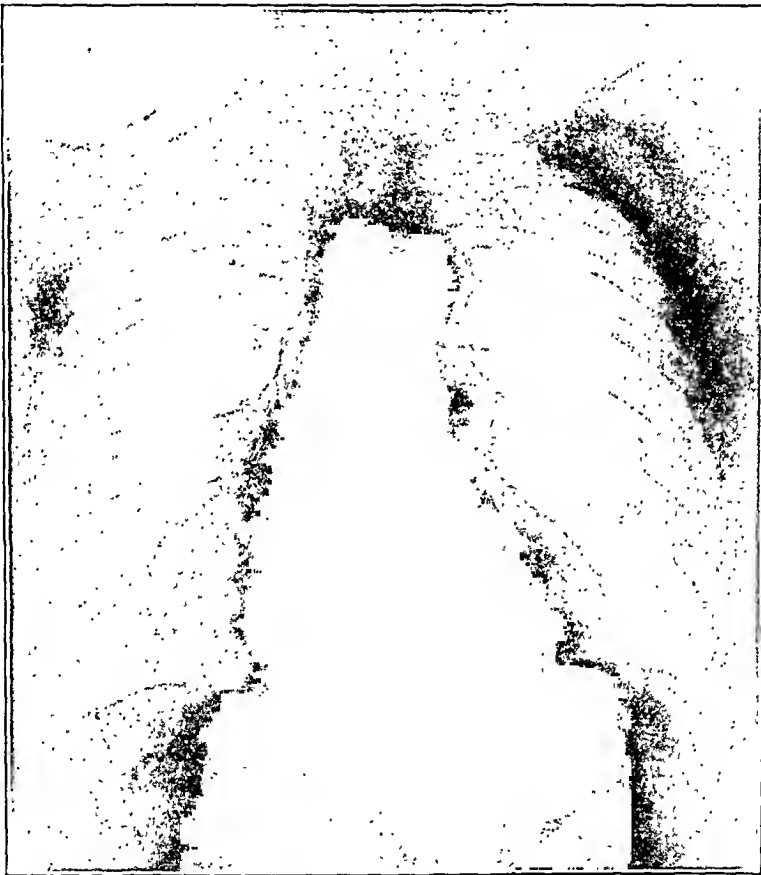


Fig. 1.—Radiogram showing the way followed by the catheter in arriving at the right auricle.

arterial shunt resulting from a congenital cardiac malformation or to a decrease of the tension of oxygen in the alveolar air, i.e., to alveolar hypoventilation.¹⁶ It has to be related to pulmonary congestion, as suggested by Meakins and Davies,¹⁷ and probably also to the alteration of the alveolar walls which Parker and Weiss¹⁸ found in their histologic study of the lungs in cases of mitral stenosis. The stasis in the pulmonary circuit disturbs the gaseous interchange between the alveolar air and the blood flowing through the pulmonary capillaries, and in spite of the increase of the tension of the alveolar oxygen, as shown by analysis of the

alveolar air, the blood leaves the lungs with a higher degree of unsaturation of oxygen. Abatement of the heart failure decreases the pulmonary stasis and the saturation of the oxygen of the arterial blood increases, as occurred in Cases 2 and 5. In Cases 16 and 17 the arterial saturation diminished considerably with increase in the degree of the heart failure, and the cyanosis was mixed (Table II).

There remains to explain the light cyanosis of the cheeks and lips, i.e., the mitral facies in Cases 18, 19, 20, and 22, in which the blood that was



Fig. 2.—Radiogram showing the catheter turned around and entered by retrograde way in the internal jugular vein in a patient with mitral stenosis.

extracted from the vein of the elbow fold and from the radial artery did not show the existence of the minimal quantity of reduced hemoglobin which is necessary for the development of cyanotic coloration (Table IV).

As Harrison¹⁹ has claimed, and Goldschmidt and Light²⁰ have shown, there may be cyanosis in heart failure by the mere dilatation of the venous capillaries. The predominance of the venous capillaries in the capillary net is the reason that the blood which is contained in them determines the coloration of the skin. As a result of this, the skin appears cyanotic even when, according to the estimate of Lundsgaard and Van

Slyke, the quantity of the reduced hemoglobin in the capillary net does not exceed minimum values.

The degree of heart failure (back pressure) and the obstacle at the level of the vena cava superior produced by the enlargement of the left auricle in mitral stenosis are held responsible for the blood stasis in the venous system and its consequence, namely, the dilatation of the venules

TABLE IV

ARTERIAL OXYGEN SATURATION AND FUNCTIONAL CAPACITY OF 4 PATIENTS WITH MITRAL STENOSIS AND "FACIES MITRAL," AND WITH REDUCED CAPILLARY HEMOGLOBIN UNDER "CYANOSIS THRESHOLD"

CASE	FUNCTIONAL CAPACITY	ARTERIAL OXYGEN SATURATION (PER CENT)	REDUCED HEMOGLOBIN CAPILLARY BLOOD (GM. PER CENT)	CYANOSIS
18	1	98.18	2.9	"Facies mitral." Nail cyanosis (+).
19	2a	98.2	3.6	"Facies mitral." Nail cyanosis (+).
20	1	98.8	4.0	"Facies mitral."
22	2a	96.9	2.1	"Facies mitral."

and venous capillaries of the face which causes the cyanotic coloration of the cheeks, chin, and lips (mitral facies), for which no increase of the reduced capillary hemoglobin is needed.

SUMMARY AND CONCLUSIONS

A study of the blood gases, alveolar air, venous pressure, and other aspects of the circulation was carried out in 22 cases of mitral stenosis, in 20 of which there were varying degrees of cyanosis. The cyanosis was due in 6 cases to a greater peripheral utilization of oxygen (peripheral cyanosis), and in 10 cases to increased peripheral utilization in the capillary net and to the increase of the oxygen unsaturation of the arterial blood (mixed cyanosis); in 4 cases the data obtained did not explain the cyanosis.

The dilatation of the small veins in the capillary net was brought on either by the venous hypertension of heart failure (back pressure), or by the increased pressure caused by an obstacle at the superior vena cava level, the presence of which was shown by catheterization of the heart; the latter may be the sole cause of the mitral facies.

We wish to express our gratitude to Professor Houssay for having allowed us to make some of the measurements of blood gases in the Department of Physiology, and to Dr. Soma Weiss for suggestions in the preparation of the manuscript.

REFERENCES

1. Corvisart, J. N.: *Essai sur les maladies et les lésions organiques du cœur et des gros vaisseaux*, ed. 2, Paris, 1818.
2. Bertin, T. J.: *Treatise on the Diseases of the Heart and Great Vessels*, American translation from French edition, Paris, 1824.

3. Bouillaud, J.: *Traité clinique des maladies du coeur*, Paris, 1841.
4. Huchard, H.: *Trattato clinico delle malattie del cuore e dell'aorta*, Italian translation from French edition, Milano, 1907.
5. Barié, E.: *Traité pratique des maladies du coeur et de l'aorte*, Paris, 1912.
6. Walshe, W.: *Practical Treatise on the Diseases of the Lungs and Heart*, London, 1851.
7. Dautrebande, L., Fetter, and Meakins, J. C.: The Blood Gases and the Circulation Rate in Cases of Mitral Stenosis, *Heart* 10: 153, 1923.
8. Cossio, P., Castillo, E. B., and Berconsky, I.: Velocidad sanguínea y capacidad funcional del corazón, *Semana méd.* 1: 1891, 1933.
9. Cossio, P., Berconsky, I., and Castillo, E. B.: L'épreuve de la vitesse sanguine a l'effort, *Bull. et Mém. Soc. méd. d. hôp. de Paris* 6: 220, 1937.
10. Haldane, J. S., and Priestley, J. G.: The Regulation of the Lung Ventilation, *J. Physiol.* 32: 225, 1905.
11. Van Slyke, D. D., and Stadie, W. C.: The Determination of the Gases of the Blood, *J. Biol. Chem.* 49: 1, 1921.
12. Lundsgaard, C., and Van Slyke, D. D.: Cyanosis, *Medicine Monographs*, Baltimore, 1923.
- 13a. Cossio, P., and Berconsky, I.: Syndrome d'hypoventilation alvéolaire, *Rev. sud-am. de méd. et de chir.* 3: 705, 1932.
- 13b. Cossio, P., and Berconsky, I.: La cyanose des malformations congénitales du coeur, *Arch. d. mal. du coeur* 28: 19, 1935.
14. American Heart Assn.: *Criteria for the Classification and Diagnosis of Heart Disease*, New York, 1932.
15. Padilla, T., Cossio, P., and Berconsky, I.: Sondeo del corazón, *Semana méd.* 2: 79, 391, 445 and 645, 1932.
16. Houssay, B. A., and Berconsky, I.: Cyanosis par l'hypoventilation alvéolaire, *Presse Médicale*, 2: 1759, 1932.
17. Meakins, J. C., and Davies, H. W.: *Respiratory Function in Disease*, London, 1925, Oliver and Boyd.
18. Parker, F., and Weiss, S.: The Nature and Significance of the Structural Changes in the Lungs in Mitral Stenosis. *Am. J. Path.* 12: 573, 1936.
19. Harrison, T. R.: *Failure of the Circulation*, Baltimore, 1935, Williams and Wilkins Co.
20. Goldschmidt, S., and Light, A. B.: A Comparison of the Gaseous Content of Blood from Veins of the Forearm and Dorsal Surface of the Hand as Indicative of Blood Flow and Metabolic Differences in These Parts, *Am. J. Physiol.* 73: 127, 1925.

CORONARY ARTERY DISEASE ANALYZED POST MORTEM

WITH SPECIAL REFERENCE TO THE INFLUENCE OF
ECONOMIC STATUS AND SEX

WILLIAM H. GORDON, M.D., EDWARD F. BLAND, M.D., AND
PAUL D. WHITE, M.D.
BOSTON, MASS.

CORONARY artery disease as a cause of disability and death has been observed to occur with greater frequency among the economically well-to-do classes. This observation has been based largely on clinical impressions and, insofar as we are aware, has not been adequately substantiated by post-mortem findings. It was for this reason that in the course of an extensive study of coronary artery disease post mortem a special investigation was undertaken.

Studies relevant to the post-mortem incidence and degree of coronary atherosclerosis have been relatively few in number,^{1, 2, 3, 4} and were made primarily to determine the influence of age, sex, and, in one instance, of race. No attempt was made, however, to note the apparent influence of "economic status" on the general incidence and distribution of the coronary artery disease.

To help in the solution of this problem, we have examined the post-mortem records of the Massachusetts General Hospital. They include a considerable number of cases from private departments (Phillips House and Baker Memorial) representing economically well-to-do patients, for comparison with cases from the public wards representing economically less fortunate members of society. We have determined the incidence and degree of significant coronary artery disease occurring in these two groups in order to test the accuracy of our clinical opinion.

It should be mentioned, however, that the patients now treated in the general wards of the Massachusetts General Hospital are not representative of the usual ward population seen in large city hospitals, or even representative of its own ward population of twenty years ago. From an economic point of view one would say that they come largely from the low middle class of wage earners, many of whom are able to pay in part for their hospitalization.

Through the courtesy of Dr. Tracy B. Mallory, we studied 3,400 consecutive post-mortem records of the Massachusetts General Hospital, dated from February, 1925, to September, 1937.* A careful examination

Received for publication July 20, 1938.

Read before the American Heart Association at San Francisco, June 10, 1938.

*During this period 3800 post-mortem examinations were made, but because of certain restrictions the heart was either not examined or by superficial palpation only. In 400 instances. Prior to February, 1925, the description of the macroscopic appearance of the coronary arteries was not always sufficiently complete to be of value in the present analysis.

of the coronary arteries and their larger branches had been recorded in each instance, along with a detailed account of the macroscopic lesions.

TABLE I
INCIDENCE AND DEGREE OF CORONARY ATHEROSCLEROSIS
3,400 Consecutive Post-Mortem Cases

AGE GROUP	TOTAL CASES	CORONARY ATHEROSCLEROSIS			
		CASES	NARROWING		
			WITHOUT OCCLUSION	WITH OCCLUSION	TOTAL
0- 20	502	5 (1.0%)	0	0	0
21- 40	575	104 (18.0%)	8 (7.8%)	7 (6.7%)	15 (14.5%)
41- 60	1,271	656 (51.7%)	162 (24.9%)	80 (12.8%)	242 (37.7%)
61- 80	990	805 (81.3%)	300 (37.2%)	109 (13.3%)	409 (50.5%)
81-100	62	59 (95.0%)	33 (56.0%)	7 (11.9%)	40 (67.9%)
Total	3,400	1629	503	203	706

POST-MORTEM DATA

As shown in Table I, the 3,400 cases were divided on the basis of age into five groups of twenty years each. For the purpose of our analysis this appeared to be a relatively simple arrangement which emphasizes the three age periods (21 to 80) of greatest clinical importance. The possibility of error in estimating the degree of coronary artery narrowing is necessarily large. In order to minimize this possibility in our comparisons, we included only cases exhibiting definite narrowing or actual occlusion of the coronary arteries which we termed "significant coronary artery disease."

Sex Relationship.—The clinically observed disproportion between the incidence of coronary artery disease in men and women is amply supported by our studies. The disproportion was greatest in young adults, the men outnumbering the women approximately three to one, with regard both to significant coronary disease and to complete occlusion. In the middle age group the disproportion was less, especially as regards uncomplicated narrowing, in respect to which our figures indicated no significant difference. In instances of occlusion, however, the men still outnumbered the women two to one. A finding of considerable interest in the study was that at the age of 70 years, and over, there was no significant sex difference in the occurrence of coronary changes.

It seems, then, that insofar as sex is concerned the factor or factors responsible for the sex disproportion in coronary atherosclerosis are most effective in young adults, less significant in those of middle age, and of little or no importance in old age. Thus, if the male survives the hazards of coronary disease in youth and middle age he is on a par with the female in this respect in old age.

Economic Status.—The presence in this series of 600 patients from the private departments of the hospital offered an opportunity for special comparative study of this important group. A large number of post-mortem examinations is necessary for the establishment of reliable generalizations; those included here will serve as a nucleus for further comparison. It is essential to examine the data in relation to the age and sex of the individual groups. Furthermore, due to the extreme rarity of significant coronary artery disease prior to the age of 20 years, and its great frequency after the age of 80 years, only those patients

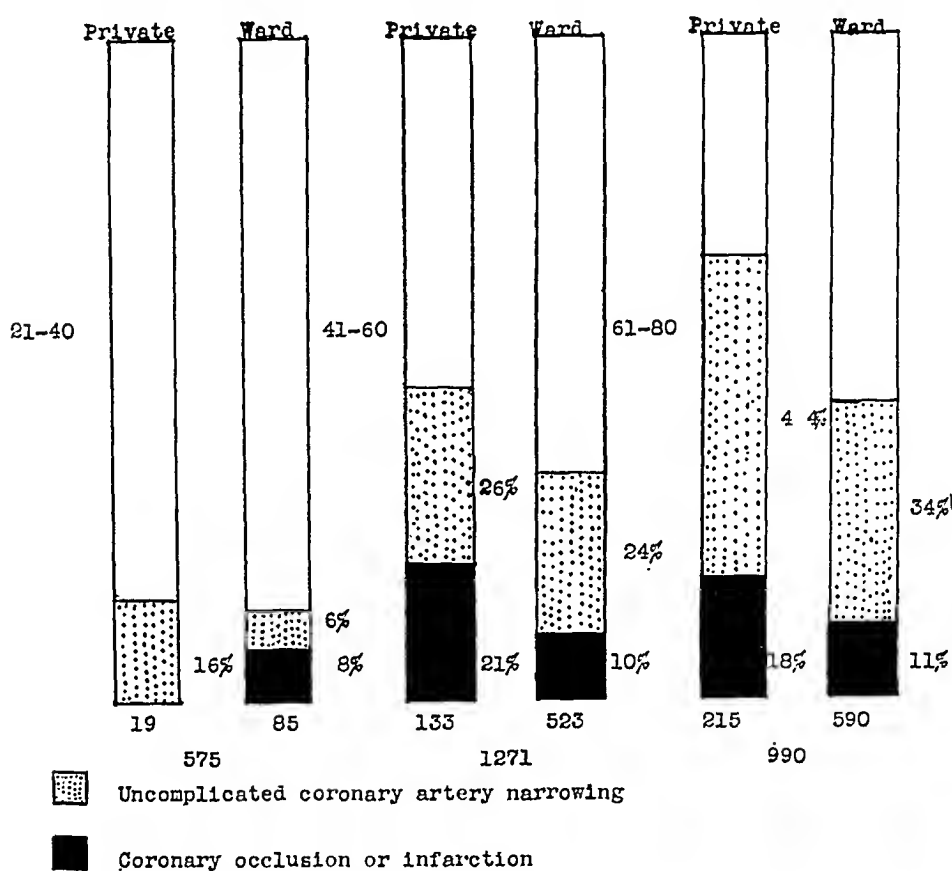


Fig. 1.—A comparison of the incidence and degree of coronary atherosclerosis on the basis of economic status.

whose age at time of death fell between 20 and 80 were included for this special study in relation to economic status.

Certain questions of a statistical nature arose when an attempt was made to analyze the material in detail. For example, it was necessary to determine whether the reasons for hospitalization and cause of death in the two groups were comparable. Also, in the course of tabulation and comparison, the number of cases occurring in certain groups was necessarily small, making it difficult to evaluate their significance. However, after making surveys of samples chosen at random from the total series, and after making computations for the determination of signif-

icance, Mr. Herbert Marks of the Statistical Bureau of the Metropolitan Life Insurance Company stated that the reason for hospitalization and the cause of death in the two groups were comparable, and that the number of patients in the groups used in the study was sufficient to serve as a basis for statistical conclusion.

The general level of coronary atherosclerosis in the private patients in all age groups was consistently greater than in those from the general wards. Furthermore, the incidence of coronary artery narrowing and occlusion follows this general trend.

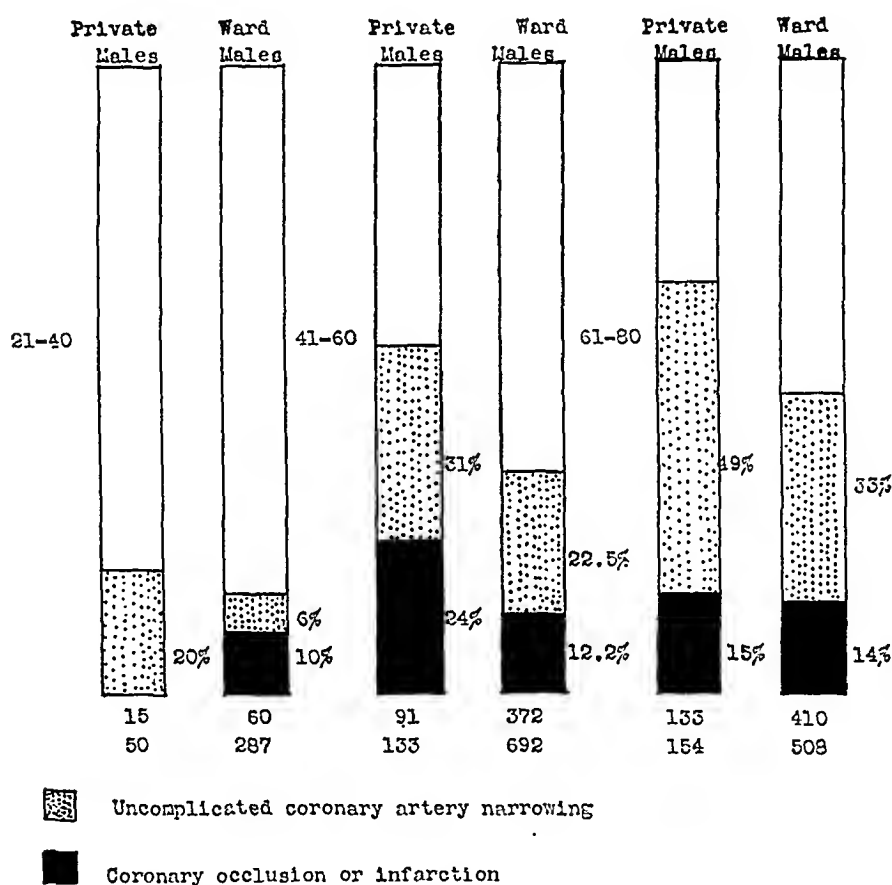


Fig. 2.—A comparison of the incidence and degree of coronary atherosclerosis in males on the basis of economic status.

In the young adults between 21 and 40 years of age the presence of seven instances of occlusion in the ward group in contrast to none in the private group is of some interest and suggests the need of further study. In spite of this finding, the incidence of recognizable narrowing of the vessels remained higher in the private patients of this age.

The most striking difference, however, between the two economic groups is reflected in the incidence of coronary occlusion in those between 41 and 60 years of age. The incidence in the private group was twice as great as in the ward group. This is a significant difference,

since the total number of post-mortem examinations in both groups for this age is considerable. The continued predominance of coronary occlusion in the private patients in the next group (between 61 and 80 years of age), although somewhat less striking, is still significant.

A further comparison of the two economic groups as regards sex necessarily reduces the number in certain instances to a level which rendered conclusions unreliable. It was justifiable, therefore, to compare only the male patients of the two groups. The greatest differences occurred in the middle age groups, in which coronary occlusion was twice as prevalent among the private patients as among those in the ward (Fig. 2).

CONCLUSIONS

In a study of the records of 3,400 consecutive post-mortem examinations made at the Massachusetts General Hospital between February, 1925, and September, 1937, the following facts were ascertained:

1. After the age of 70 years there was no difference in the incidence of coronary artery disease in men and women. Before that age there was much more in men than in women.

2. The relative incidence and the degree of coronary atherosclerosis were found to be significantly greater in the 600 patients from the private departments than in the 2,800 patients from the general wards. The greatest difference occurred in the middle-aged patients, in whom coronary occlusion was found to be twice as frequent in the private group. This difference was most striking in the middle-aged males. These findings are in general agreement with clinical impressions.

REFERENCES

1. Levy, R. L., Bruenn, H. G., and Kurtz, Dorothy: Facts on Disease of the Coronary Arteries Based on a Survey of the Clinical and Pathologic Records of 762 Cases, *Am. J. M. Sc.* 187: 376, 1934.
2. Willius, F. A., Smith, H. L., and Sprague, P. H.: A Study of Coronary and Aortic Sclerosis; Incidence and Degree in 5060 Consecutive Post-Mortem Examinations, *Proc. Staff Meeting of Mayo Clinic* 8: 140, 1933.
3. Allan, G. H.: Diseases of Coronary Arteries, *Brit. M. J.* 2: 232, 1928.
4. Johnston, Christopher: Racial Difference in the Incidence of Coronary Sclerosis, *AM. HEART J.* 12: 162, 1936, pp. 162-167.

THE ISOLATION OF NICOTINE FROM HUMAN URINE*

O. M. HELMER, PH.D., K. G. KOHLSTAEDT, M.D., AND
IRVINE H. PAGE, M.D.
INDIANAPOLIS, IND.

NICOTINE usually elevates arterial blood pressure in man when it is absorbed in sufficient amounts from tobacco smoke. When it is injected into cats or dogs it causes powerful vasoconstriction and rise of arterial pressure. Since it is absorbed in large quantities daily by countless people, it is a matter of importance to ascertain its fate in the body. We have examined urine for its presence.

EXPERIMENTAL

Method of Extracting Pressor Substance From Urine.—Urine was collected from normal persons. It was made alkaline with sodium hydroxide (1 to 2 gm. of sodium hydroxide per liter) and extracted with ether in continuous extractors (two-liter capacity) for twenty-four hours. The ether extract was transferred to separatory funnels, washed with distilled water, and extracted three times with 0.1 N hydrochloric acid (about one liter of acid for a forty-eight-hour urine specimen).

The hydrochloric acid extract was reduced to small volume by means of vacuum distillation, transferred to a small beaker, and evaporated to dryness on a steam bath to remove the last traces of hydrochloric acid. The dry residue was taken up in 0.9 per cent sodium chloride solution, adjusted to neutrality with one N sodium bicarbonate solution, and made up to a standard volume of 6 c.c. From 0.1 to 1 c.c. of this extract was used for the assay.

In addition, pressor extracts were prepared by extraction of alkaline urine with benzene instead of ether. Active extracts were also obtained by adsorption and elution from animal charcoal by the technique described by Bain.¹

Methods of Preparing Animals.—Arterial pressure was measured in cats weighing 2 to 3 kg. by inserting a cannula into a carotid artery and connecting it to a mercury manometer, using heparin as anticoagulant. The remaining carotid artery was ligated; both vagi were cut and a tracheal cannula was inserted for artificial respiration. The cat was now decerebrated on the Sherrington guillotine. Some animals were pithed after decerebration and others were pithed without being decerebrated. A pithed cat anesthetized with pentobarbital (33 mg. per kg. intraperitoneally) was found to be most satisfactory for assay of the pressor effect of urine extracts. The material to be tested was injected into a femoral vein.

A few experiments were carried out on dogs prepared in a similar manner, using paraldehyde (1.7 c.c. per kg.) as the anesthetic.

Pressor Effects of Extracts of Urine and of Oxalates and Picrates Prepared from These Extracts.—Numerous extracts of pooled urine specimens which were collected from normal men were prepared. Extracts made by ether extraction gave most uniform effects on the blood pressure of pithed cats (Fig. 1A).

*From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis.

Received for publication July 20, 1938.

Solutions of crystalline derivatives (oxalate and pterate) of the pressor principle prepared from large quantities of normal urine produced an elevation of arterial pressure similar to that obtained from crude urine extracts. Comparable injections into the same animal revealed that the crystalline derivatives from urine extract were approximately as active as nicotine (Fig. 2). The supernatant fluid after removal of oxalate or pterate crystals produced no rise in arterial pressure. Likewise, solutions of sodium oxalate or pterate were found to have no pressor effect.

Comparing portions of the same extract, there was no difference in the height of the blood pressure rise produced in cats under ethyl urethane (subcutaneously), paraldehyde (orally), ether (inhalation), or pentobarbital (intraperitoneally) anesthesia. Greater rises in arterial pressure were produced in cats which were either decerebrated or pithed than in the intact animal, but there was no appreciable difference between decerebrated and pithed animals.

When 8 mg. of cocaine were previously injected as a sensitizing agent, the rise in blood pressure produced by the same dose of urine extract was neither augmented nor inhibited, although this amount of cocaine doubled the response to adrenin and partially inhibited the action of tyramine. The pressor effect of urine extracts was not reversed to depressor by previous injection of ergotoxine. The urine extract differed from adrenin and tyramine in that when injections were rapidly repeated (at intervals of less than fifteen minutes) the animals soon became refractory. About forty minutes were required to restore the original degree of reactivity.

Bilateral adrenalectomy did not alter the responsiveness of pithed cats to the action of urine extracts (Fig. 1A).

Other Pharmacologic Properties.—Contractions of the nictitating membrane were regularly produced by injection of extracts which simultaneously produced a marked rise of arterial pressure. Greater contractions of the nictitating membrane were obtained with tyramine than with urine extracts, although the rise in arterial pressure was less. Large doses of extracts (1 to 2 c.c.), when given to intact or decerebrated animals, often produced twitchings of voluntary muscle, vomiting, defecation, convulsions, and death.

Comparative Study of Individual Forty-Eight-Hour Urine Specimens.—Extracts of forty-eight-hour urine specimens obtained from a group of twenty-two normal men were tested several times on different cats and the average rise of blood pressure produced by 0.5 c.c. of each extract was calculated. Some of these extracts were also tested on dogs. The dogs were given 2.0 c.c. of extracts from nonsmokers and 0.2 c.c. of extracts from those who smoked. (All extracts were prepared so that 6 c.c. of the extract were equivalent to the total forty-eight-hour urine

specimens.) Much larger rises in blood pressure were produced by extracts obtained from the men who smoked than from those who indulged occasionally or not at all (Table I).

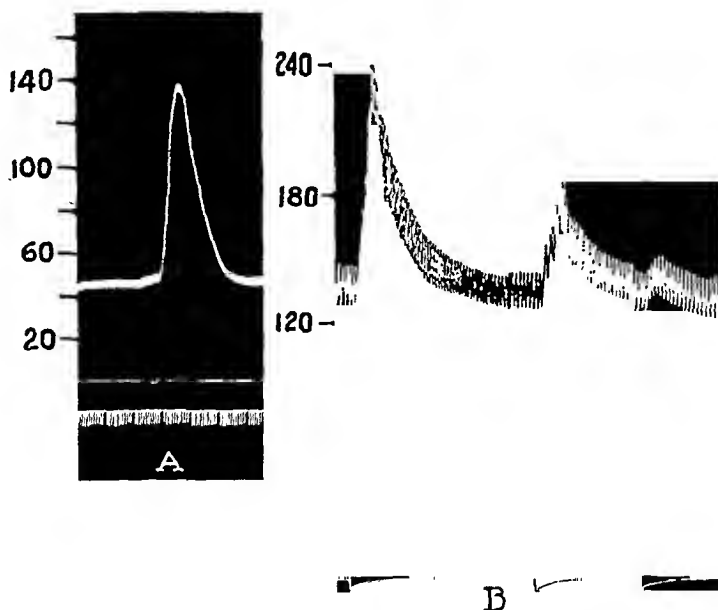


Fig. 1.—*A*, The effect of 0.8 mg. of nicotine picrate crystals prepared from pooled normal urine given intravenously to an adrenalectomized pithed cat under pentobarbital anesthesia. *B*, The effect of intravenous injection in a dog under paraldehyde anesthesia with vagi cut of (1) 0.3 c.c. of urine extract from period in which forty cigarettes were used, (2) 0.3 c.c. of urine extract from first twenty-four hours in which no tobacco was used, and (3) 0.3 c.c. of urine extract from the second twenty-four-hour period after smoking had been stopped.

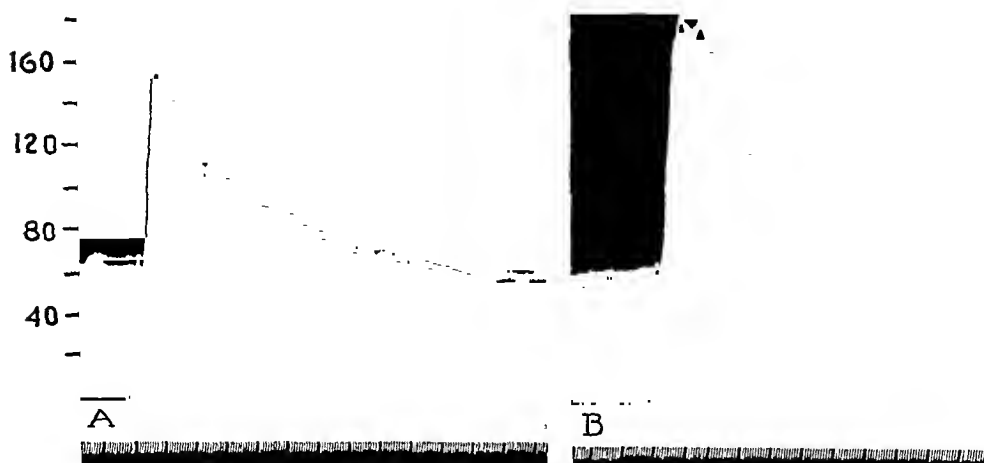


Fig. 2.—The effect of (*A*) the intravenous injection of 1.2 mg. of nicotine picrate crystals from pooled normal urine into pithed cat under pentobarbital anesthesia, and of (*B*) the intravenous injection given forty minutes later of 1.2 mg. of nicotine.

The effect of stopping the use of tobacco on the amount of nicotine extracted from the urine was demonstrated by withholding cigarettes for a forty-eight-hour period from one subject who regularly smoked

forty cigarettes a day, and collecting twenty-four-hour urine specimens during this period. In the same dog, a much smaller rise in blood pressure was produced by extracts of urine collected during nonsmoking periods than by the extract of urine collected when the subject was smoking his usual number of cigarettes (see Fig. 1B).

TABLE I

THE EFFECT OF INJECTION OF URINE EXTRACT ON BLOOD PRESSURE OF PITHED CATS AND INTACT DOGS

		AMOUNT OF TOBACCO USED PER 24 HOURS	AVERAGE RISE IN BLOOD PRESSURE (MM. HG)	NUMBER OF EXTRACTS TESTED
<i>Cats:</i>				
Nonsmokers or occasional smokers (0.5 c.c. of extract given)	Occasional cigarette		21	11
	Occasional pipe		37	4
	Total abstinence		33	3
	Total abstinence		35	3
	Total abstinence		38	3
	Total abstinence		34	1
	Total abstinence		11	1
	Total abstinence		4	2
Smokers (0.5 c.c. of extract given)	40-50 cigarettes		270	5
	40-50 cigarettes		183	2
	40 cigarettes		250	4
	40 cigarettes		190	2
	30 cigarettes		210	6
	30 cigarettes		131	3
	30 cigarettes		93	4
	20 cigarettes		135	5
	20 cigarettes		156	1
	20 cigarettes		112	2
	20 cigarettes		100	1
	20 cigarettes		73	2
	20 cigarettes		30	2
	4-5 cigars + pipe		134	1
<i>Dogs:</i>				
Nonsmokers or occasional smokers (2.0 c.c. of extract given)	None		6	1
	None		8	1
	None		4	1
	None		10	1
	None		8	1
	None		2	1
	None		4	1
	None		10	1
	None		8	1
	None		10	1
Smokers (0.2 c.c. of extract given)	40 cigarettes		30	1
	50 cigarettes		24	1
	50 cigarettes		38	1
	4 cigars + pipe frequently		33	1

Isolation and Identification of Nicotine from Normal Urine.—The urine was made alkaline with sodium hydroxide and extracted in a continuous ether extractor of large capacity (20 liters). The ether extract was washed with distilled water in a separatory funnel and extracted three times with 0.1 N hydrochloric acid. The hydrochloric acid extract was concentrated to a small volume by vacuum distillation. It was made alkaline by sodium hydroxide in the cold. The alkaline extract was steam-distilled until the distillate no longer gave a precipitate with silicotungstic acid. The distillate was extracted in a separatory funnel with ether until the

aqueous phase no longer gave a precipitate with silicotungstic acid. The combined ether extracts were dried with anhydrous sodium sulfate and filtered through paper. A solution of anhydrous oxalic acid in anhydrous ether was then added to the clear, colorless solution until precipitation was complete. The solution was allowed to stand in the icebox overnight.

The oxalate was dissolved in a small quantity of warm absolute alcohol and allowed to stand in the icebox for twenty-four to forty-eight hours. A crystalline oxalate deposited which had only a slight pressor activity. A further precipitate could be obtained by the addition of dry acetone. This oxalate was strongly pressor. A sticky residue was obtained on evaporation of the mother liquors which also had strong pressor properties. The oxalates failed to give sharp melting points, hence they were converted into picrates. The oxalates precipitated by acetone and the one recovered by evaporation were dissolved in water, made alkaline with sodium hydroxide, and again subjected to steam distillation. The distillate was transferred to a separatory funnel and extracted with ether. The ether solution was dried with anhydrous sodium sulfate and filtered. Alcoholic solution of picric acid was added and the precipitate recrystallized from warm alcohol. A light yellow crystalline picrate was obtained. The following data showed that it was nicotine picrate.

Nicotine picrate prepared from nicotine melted at 215 to 216.5° (uncorrected). A mixture of picrate prepared from urine (2.5 mg.) and nicotine picrate (2.5 mg.) melted at 215 to 216° (uncorrected). The results of analysis of the urine picrate are given in Table II.

TABLE II

	PICRATE FROM URINE (%)	CALCULATED FOR NICOTINE PICRATE (%)
C =	42.64	42.57
H =	3.18	3.25
N =	18.00	18.06

DISCUSSION

It has been shown that nicotine can be isolated in crystalline form as oxalate or picrate from the urine of human beings who smoke tobacco.* The pharmacologic properties of the substance isolated from urine are identical with those of pure nicotine. If tobacco smoking is discontinued, nicotine almost disappears from the urine within three to four days.

It has been known for many years that the injection of urine or extracts of it into anesthetized animals often produces a rise in arterial pressure. This has formed the basis of much speculation concerning the association of urinary pressor substances with the genesis of hypertension. Extracts of urine have been studied by several investigators,^{1, 2, 3} but it is not always possible to ascertain from the description of the method of preparation whether the pressor substance was nicotine. In some cases it probably was.

It is understandable why much confusion exists concerning the results of urine examination for pressor substance from patients with hyper-

*Extracts of blood which appear to contain nicotine have also been prepared.

tension. In some, smoking was probably strictly interdicted, as for example, during hospitalization, while in others, as a result of confinement and emotional disturbance, indulgence was greater. Since the substance responsible for a large part of the pressor activity of urine extracts is nicotine, the relation of pressor activity to the condition of the patient would depend chiefly on whether tobacco was being used.

Little is known of the metabolism of nicotine. Biebl, Essex, and Mann⁴ showed in heart-lung preparations from dogs that the ability of liver to destroy nicotine was greater than an equivalent mass of hind limb, and that the action of a comparable dose of nicotine on the blood pressure of a dog was much more pronounced after hepatectomy than before. It has been suggested that nicotine might be excreted in urine, but the evidence for it has rested chiefly on the observation that extracts of urine or organs cause contraction of leech muscle.^{5, 6} Perez⁷ has attempted to determine nicotine in urine by silicotungstic acid. It is difficult to say how successful he was because there appears to be no record of the amount he could recover by his method or how much was pure nicotine. He has shown wide variation in the nicotine content of various tobaccos, and suggested that nicotine might be retained in the body when renal function was reduced.

SUMMARY

1. Nicotine has been isolated as crystalline oxalate and picrate from the urine of persons who smoke. Its pharmacologic properties are the same as those of pure nicotine.

2. Most of the nicotine disappears from the urine within three to four days after smoking has been discontinued.

3. Nicotine appears to be the substance responsible for the marked pressor action of many urine specimens. Unless tobacco has been eliminated as a source of pressor substance in urine, conclusions relating urinary pressor substances to arterial disease may not justifiably be drawn.

REFERENCES

1. Bain, W.: I. Pressor Bases in Normal Urine and Their Diminished Excretion in Gouty Urine, *Lancet* 2: 365, 1909; Further Work on the Pressor Bases of the Urine, *Lancet* 1: 1190, 1910.
2. Abelous, J. E., and Bardier, B.: Sur l'Urohypertensive et L'action Sialogène de L'urine, *Compt. rend. Soc. de biol.* 65: 63, 1908.
3. Bohn, H., and Hahn, F.: Blutdrucksteigernde Stoffe im Harn, insbesondere beim blassen und roten Hochdruck, *Ztschr. f. klin. Med.* 123: 558, 1933.
4. Biebl, M., Essex, H. E., and Mann, F. C.: The Role of the Liver in the Destruction or Inactivation of Nicotine, *Am. J. Physiol.* 100: 167, 1932.
5. Nöther, P.: Quantitative Studien über das Schicksal des Nikotins im Organismus nach Tabakrauchen, *Arch. f. exper. Path. u. Pharmacol.* 98: 370, 1923.
6. Emanuel, W.: Über das Vorkommen von Nicotin in der Frauenmilch nach Zigaretten-genuss, *Ztschr. f. Kinderh.* 52: 41, 1931-32.
7. Perez, L. C.: Dosificación de la Nicotina en el Humo de los Cigarros et en la Orina de los Fumadores, *Arch. latino am. de cardiología y hemat.* 7: 71, 1937.

TISSUE PRESSURE: AN OBJECTIVE METHOD OF FOLLOWING SKIN CHANGES IN SCLERODERMA

WILLIAM A. SODEMAN, M.D.,* AND GEORGE E. BURCH, M.D.*
NEW ORLEANS, LA.

THERE has been no satisfactory objective method of estimating the effect of therapeutic procedures on the skin changes in scleroderma. We believe that the estimation of tissue pressure may be used in this way. The hardened and slowly contracting skin would be expected to have a direct effect upon the tissue pressure, particularly in the extremities where pressure is brought to bear upon the encased tissues from all sides. While making observations on this pressure in the subcutaneous tissue in patients with vascular disease, we found elevated values in scleroderma,¹ indicating that changes in tissue pressure might be used as an index of the progress of the disease. The present study was undertaken to evaluate this relationship.

The method has been described elsewhere.² It consists (Fig. 1) essentially of a U-tube water manometer (*a*) which is connected by rubber tubing (*b*) to a rubber pressure bulb (*c*) controlled by a screw clamp (*d*) and also connected to a 1.0 mm. bore glass adapter (*e*) to which is fastened a 27-gauge needle (*f*). Parallel lines, etched at millimeter intervals in the wall of the adapter, facilitate reading of slight movement of the meniscus. The beveled end of the needle was occluded with solder and four openings symmetrically drilled into the lumen through the wall of its distal third. In use, sterile normal saline was drawn into the needle and about half the way up the adapter, and the pressure in the system brought to atmospheric. The needle was then inserted into the subcutaneous tissues of the part to be studied. The pressure in the system was slowly raised by the screw clamp until the meniscus in the adapter just began to move. This pressure was taken as the subcutaneous tissue pressure. Aseptic technique was used throughout.

We have previously reported the normal range of tissue pressure for the common edema sites.² The values are summarized in Table I. The maximum value in any site was found to be 54 mm. of water at heart level. Elevations in venous pressure were found to influence tissue pressure. The full effect of venous pressure was not immediate; for short periods of time the effect was slight, but when prolonged, as in congestive heart failure, the tissue pressure was greatly elevated. Indeed, in all types of increasing edema studied, the tissue pressure was invariably elevated. However, in receding edema, the values were lowered, at times even below normal, to return finally to a normal level.² Thus far, in the absence of edema or increased venous pressure we have not found an elevation in tissue pressure except in scleroderma. Other conditions may exist, for example, in an area in which there is increased intrinsic or extrinsic pressure.

*From the Department of Medicine, School of Medicine, Tulane University of Louisiana, and from the Charity Hospital of Louisiana, New Orleans.

Received for publication July 20, 1938.

TABLE I

SUBCUTANEOUS TISSUE PRESSURE (MM. H₂O) AT HEART LEVEL IN TEN NORMAL SUBJECTS

	DORSUM OF HAND	VOLAR SURFACE OF FOREARM	PRETIBIAL AREA	DORSUM OF FOOT
Mean	17.9	23.6	37.1	30.8
Maximum	30.0	40.0	54.0	43.0
Minimum	8.0	11.0	18.0	15.0

In seven patients with scleroderma we have found the subcutaneous tissue pressure to be elevated in the affected areas. The values varied from 338 to 26 mm. of water, the initial readings in these seven patients being 280, 234, 136, 76, 74, 34, and 28. Comparison of the mean values

TABLE II

TISSUE PRESSURE IN SEVEN PATIENTS WITH SCLERODERMA (MM. H₂O)

NO.	AGE AND SEX	SITE	REMARKS							
			4/22/37	4/23/37	4/28/37	5/ 4/37	6/17/37	8/24/37	5/31/38	
1	21 F	Right forearm	280	Right cervical Sympa- thec.	Edema 338	Parathy- roidec- tomy	216	128	112	
2	40 F	Right forearm	8/24/37 234	8/25/37	9/30/37	11/11/37 240 320				
		Left forearm	50	Left cervical Sympa- thec.	Mild edema 68	76				
3	9 F	Left pre- tibial	7/ 8/37 74	7/15/37 Left lumbar Sympa- thec.	11/ 9/37 180	3/18/38 134	5/13/38 108			
4	52 M	Dorsum Right hand	2/16/38 28	2/17/38 Thyroid extract started	4/11/38 34					
		Dorsum Left hand	26		26					
5	29 M	Dorsum Right hand	76							
6	48 M	Dorsum Right hand	136							
7	42 F	Dorsum Right hand	12/18/37 34	5/30/38 26						
		Dorsum Left hand	28	38						

with the normal is illustrated in Fig. 2. The values not only varied from patient to patient but also from region to region in the same patient, depending upon the degree of the process (Table II). For

example, in one patient (No. 2), with areas of calcification and with localized patches in which the sclerodermatous process was more marked than in the surrounding skin, the tissue pressure varied considerably. In one of these thickened areas in the right forearm the tissue pressure was found to be 320 mm. of water, while in a less involved nearby area the value was 240. In the opposite, less severely involved arm, the value was found to be 76 mm. of water. It appeared, therefore, that the tissue pressure varied with the degree of involvement.

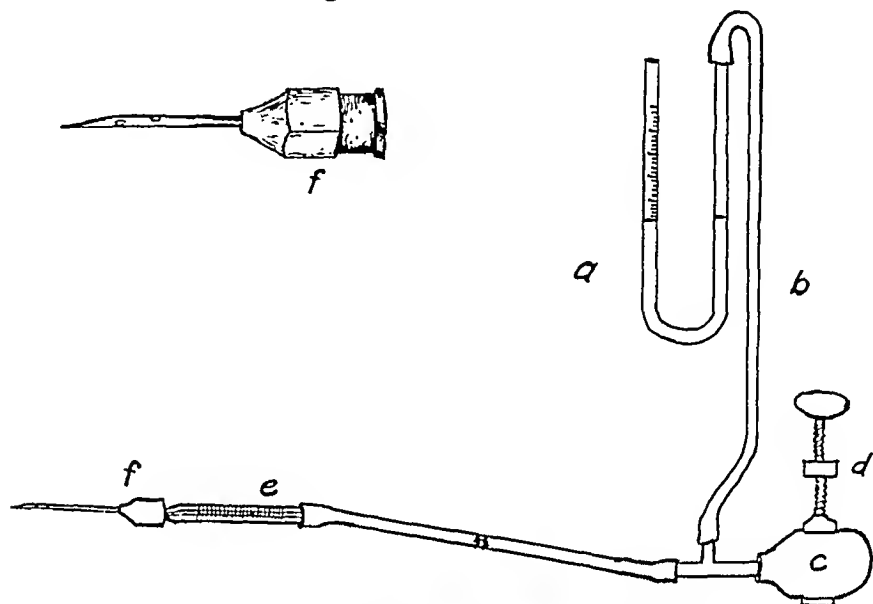


Fig. 1.—The tissue pressure apparatus (see text).

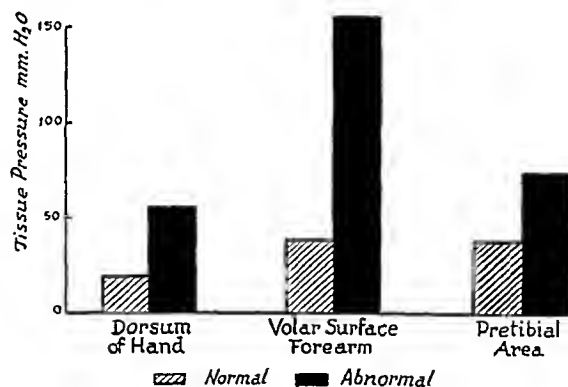


Fig. 2.—Mean initial determinations in seven patients with scleroderma, compared with mean normal values.

A similar relationship was found from patient to patient. In patients No. 4 and 7, with early changes, tissue pressure was found to be within the upper limits of normal, while in patient No. 5, with more marked involvement, the value was distinctly elevated. Again, in patient No. 6, with a still more marked process, the pressure was found to be even higher.

Not only does tissue pressure serve as an objective method for determining the degree of the sclerodermatous process, but it may also

serve as a method for quantitatively measuring the degree of change in the involved area from time to time, with or without the influence of therapeutic measures. In a typical patient (No. 1), followed for thirteen months, distinct changes were noted in the subcutaneous tissue pressure. The value in the dorsum of the right forearm, which was markedly involved, was 280 mm. of water. Five days later, following a right stellate ganglionectomy, the value rose to 338 mm. of water. At this time the patient had edema of the entire right arm. A parathyroidectomy was performed eleven days later. Six days following this operation, the tissue pressure was found to be 216 mm. of water, and nine weeks later it had dropped to 128 mm. of water. Clinically, as well, the patient had improved. All determinations were made in the same area. That the procedure may also follow the increased severity of the disease is exemplified by patients No. 2 and 3 in whom, in spite of therapeutic procedures, the initial values of 50 and 74 mm. of water increased to 76 and 180 mm. of water, respectively.

Patients have not yet been followed sufficiently long to evaluate the merits of various therapeutic procedures, and the present report is limited to a demonstration that measurement of tissue pressure may be used as an objective method of following these changes. A detailed report of results and an evaluation of therapeutic procedures, together with other physiologic observations, will be published at a later date in collaboration with the Department of Surgery.

COMMENT

There is much indirect evidence³ to indicate that the contracting skin of scleroderma increases the pressure on the underlying structures. The appearance of the skin and the pathologic changes in the underlying structures have long indicated this possibility (Fig. 3). As early as 1898, Osler⁴ described the patient as "encased in an ever shrinking, slowly contracting skin of steel." The skin is stretched and smooth, with obliteration of the ridges and sulci. As Mayo and Adson⁵ state, the changes, such as cyanosis, swelling, pain, atrophy, contraction, deformities, and disuse, simulate those that arise from a plaster cast that is too tight. The skin is pale, particularly over the prominences when the hand is flexed. Furthermore, it has been noted,³ and this was well shown in one of our patients, that extension of the fingers resulted in ischemia of the finger pad, an indication of the tightness of the skin. Further indirect evidence of the increased pressure on the underlying tissue is the disturbance in circulation. Skin temperature and pulsatile phenomena are diminished in the involved areas, apparently as a result of the increased pressure upon the blood vessel walls. Our direct determinations of the subcutaneous tissue pressure substantiate this belief. As far as we know, this is the first time that increased pressure in the subcutaneous structures has actually been directly demonstrated in this

disease. Since the phenomena accompanying the increased pressure appear to parallel the severity of the disease, we have available now a direct method whereby we may not only follow the general course of the disease, but also the variations in the severity of the process in different areas. It is obvious that a rise in tissue pressure may occur before the process is manifest clinically. Under such circumstances tissue pressure determinations may lead to a diagnosis of sclerodermatous changes before the disease may be recognized in that patient or in a particular area by other methods.

It is well known that vascular changes may precede the development of scleroderma and also that such changes may be secondary to the sclerodermatous process. Our results give direct evidence upon a mechanism of the latter type. With tissue pressures of the magnitude which we have found, which have exceeded the normal venular and capillary

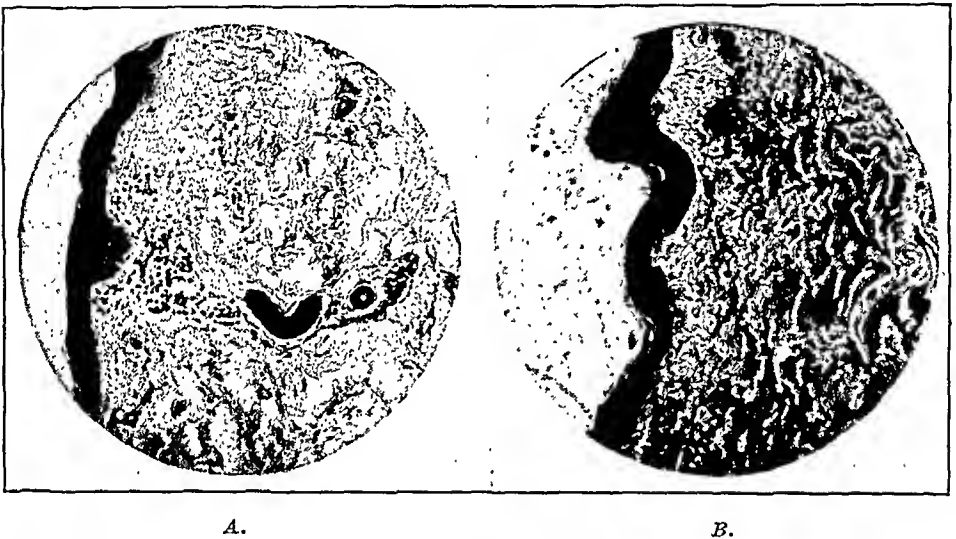


Fig. 3.—Section of normal skin (A) and sclerodermatous skin (B), showing the differences in quality and quantity of dermal structures.

pressures, one would expect a collapse of these vessels. Permanent collapse would be prevented by a building up of the venular and capillary pressures from the arteriolar side, provided no collateral circulation were possible. It is conceivable that in a localized area, if the process were severe, and if a collateral circulation were adequate, a rise in tissue pressure, exceeding the venous pressure and the pressure of the adjoining tissues, could result in localized ischemia and atrophy. Proximal to the involved areas in which the tissue pressure exceeds the normal venous pressure, the venous pressure would fall to its usual normal value. This is exemplified by the conditions existing when a pneumatic cuff about the upper arm is inflated to a value exceeding the normal venous pressure and less than diastolic blood pressure. In such an instance the venous pressure distal to the cuff will build up and equal the cuff pressure to re-establish the circulation, while the venous pres-

sure proximal to the cuff is unaffected. As a routine measure, venous pressure measurements are difficult in these patients because of the character of the skin and the small size of the veins in the involved areas. Fortunately, however, a small vein was accidentally entered while taking the tissue pressure in the dorsum of the arm in one of our patients. The venous pressure in this vein at heart level was 228 mm. of water, while the pressure at heart level in the uninvolved anticubital space was 86 mm. of water. Such direct venous pressure determinations made with the tissue pressure apparatus are extremely accurate, as we have shown elsewhere.⁶

Such an interrelationship of tissue pressure and intravascular pressure would demand that a rational approach to the treatment of scleroderma include measures which tend to reduce the tissue pressure in these subjects. We are at present engaged in studying certain aspects of this problem.

SUMMARY AND CONCLUSIONS

1. The determination of tissue pressure may be used as an objective method for evaluating changes in the skin of patients with scleroderma.

2. The subcutaneous tissue pressure at heart level in the involved areas in seven patients with scleroderma was found to vary from 26 to 320 mm. of water in the absence of edema. In normal individuals comparable determinations have never exceeded 54 mm. of water.

3. The effect of the increased tissue pressure of scleroderma upon the contained blood vessels has been discussed.

4. Since the subcutaneous tissue pressure can be objectively determined and recorded by this method, and since this pressure has been found to vary with the severity of the sclerodermatous process, it offers promise as a guide to the effectiveness of therapeutic procedures. The method also offers a diagnostic aid in patients suspected of scleroderma when clinical findings are minimal and before subjective symptoms have become prominent.

REFERENCES

1. Sodeman, W. A., and Burch, G. E.: Tissue Pressure in Subcutaneous Edema, *Am. J. M. Sc.* 194: 846, 1937.
2. Burch, G. E., and Sodeman, W. A.: The Estimation of Subcutaneous Tissue Pressure by a Direct Method, *J. Clin. Investigation* 16: 845, 1937.
3. Prinzmetal, M.: Studies of the Mechanism of Circulatory Insufficiency in Raynaud's Disease in Association With Sclerodactylia, *Arch. Int. Med.* 58: 309, 1936.
4. Osler, W.: On Diffuse Scleroderma, With Special Reference to Diagnosis, and to the Use of Thyroid-Gland Extract, *J. Cutan. and Genito-Urin. Dis.* 16: 49, 127, 1898.
5. Mayo, W. J., and Adson, A. W.: Raynaud's Disease, Thromboangiitis Obliterans and Scleroderma; Selection of Cases for and Results of Sympathetic Gangliectomy and Trunk Resection, *Ann. Surg.* 96: 771, 1932.
6. Burch, G. E., and Sodeman, W. A.: A Direct Method for Determination of Venous Pressure; Relationship of Tissue Pressure to Venous Pressure, *J. Clin. Investigation*, January, 1939.

THE POSTPHLEBITIC VARICOSE ULCER

SURGICAL TREATMENT WITH SPECIAL REFERENCE TO THE COMMUNICATING VEINS OF THE LOWER LEG*

ROBERT R. LINTON, M.D., AND J. KENNETH KEELEY, M.D.
BOSTON, MASS.

IN GENERAL there are two types of ulceration of the lower leg associated with varicose veins. This was pointed out originally by Homans,¹ in 1917. The first type is the simple varicose ulcer which is found in association with a varicose and incompetent condition of the long or short saphenous veins. They are readily healed by the obliteration of the varicose veins by multiple injections of a sclerosing solution into the involved veins, or better by high ligation of the long or short saphenous veins in addition to the injections. The second type, the postphlebitic varicose ulcer, is the ulceration which may develop on the lower leg from one to twenty years after a thrombophlebitis that has involved the deep veins of the leg. In contradistinction to the simple varicose ulcer, this type is characterized by its chronicity and the difficulty of obtaining a cure. The long or short saphenous veins or both of them are usually found incompetent in the postphlebitic leg. In addition, some or all of the communicating veins of the leg which connect the deep system of veins with the superficial ones are found to be incompetent. Thus, if the Trendelenburg test is carried out it will be found that the superficial veins of the lower leg fill rapidly from the deep veins through the communicating veins as well as from superficial ones. It is felt that the incompetence of the communicating veins explains the difference between these two types of ulcers.

An antecedent history of deep phlebitis cannot be elicited in all patients with this type of ulceration. However, in most cases one gets a history that at some time previous to the appearance of the ulcer the patient developed a swollen leg following pregnancy, an operation, a serious illness, or severe trauma to the extremity. The appearance of the ulceration and the skin surrounding it is very characteristic. Frequently the actual ulceration will be only a few centimeters in diameter, although in long-standing cases it may completely encircle the leg. When the patient seeks medical treatment the ulcer is covered with a dirty exudate from which a variety of organisms may be cultured. Sometimes hemolytic streptococci are present, but as a rule they are not. The skin about the ulcer for a distance of 5 to 10 cm. presents a purplish cyanotic hue when the leg is in a dependent position. A dark brownish pigmentation

*From the Peripheral Vascular Clinic of the Massachusetts General Hospital, Boston.

Received for publication July 20, 1938.

of the skin is seen in cases of long-standing ulceration. The more central portion of the skin frequently has an edematous, hypertrophied appearance. After removal of a dressing over the ulcer it is not uncommon to observe many droplets of clear, amber-colored fluid form on the discolored skin. On palpation of the leg it is found that there is a brawny edema of the subcutaneous tissues which may encircle the leg from the level of the malleolus to just below the knee. More commonly the edema is localized to the inner aspect of the lower leg. There is usually a very sharp line of demarcation between the normal and the edematous tissues. In many cases due to the edema, and in others to fibrous tissue beneath the skin, it may be impossible to see or palpate the varicose veins. Frequently they are felt as soft elastic channels running through the brawny and fibrous subcutaneous tissues.

The present forms of treatment of the postphlebotic varicose ulcer leave much to be desired. They may be divided into two types. The first are conservative procedures which may be termed "temporary healing measures." They consist in the use of elastic bandages,² paste boots and chemical applications such as gentian violet,^{3, 4} balsam of Peru, pastes and ointments of various materials, the injection of sclerosing solutions into the varicose veins,⁵ and the electrical method of iontophoresis with acetyl-beta-methylcholine chloride.⁶ It would be an unusual year in which no new types of ointments or chemicals were described in the medical literature. The multiplicity of these remedies is sufficient evidence of the ineffectiveness of all of them.

The second type of treatment consists of surgical methods. These are chiefly the use of skin grafts either with or without excision of the ulcer. They have been described by Mayo,⁷ Homans,¹ Trout,⁸ Brown, et al.,⁹ Pennoyer,¹⁰ and Douglas.¹¹ The results by excision and skin grafting in our clinic have been gratifying in many cases, especially those done by Homans' technique. Nevertheless, there are a certain number of failures and recurrences. Because of the unsatisfactory results with both the conservative and surgical methods of treatment a careful analysis of the cause of these ulcers was made. As a result of this study a new form of treatment was developed.

The method that was devised is divided into five steps. The first one is the healing of the ulceration. This is accomplished by putting the patient to bed and elevating the affected leg on pillows so that it is at, or slightly above, the level of the heart. Warm compresses of a 2 to 4 per cent boric acid solution are applied to the ulcer area every two hours. If hemolytic streptococci are present, compresses of a surgical solution (Dakin's) of chlorinated soda are used. In some cases, when the ulcer is small, it will heal spontaneously under this regime. When the larger ulcerations become sufficiently clean, usually within one or two weeks, they are covered with Thiersch skin grafts. After ten days to two weeks the grafts will have taken solidly, and then the patient is ready for the

second step in the treatment. This consists in the ligation of the long saphenous vein of the affected limb at the saphenofemoral junction in the groin. If the ulcer is located on the posterolateral surface of the leg the short saphenous vein is ligated at the saphenopopliteal junction in the popliteal space. These operations are done under 1 per cent novocain infiltration anesthesia a few days before the patient is to be discharged from the hospital. It is important to ligate these veins at this time because it helps keep the ulcer from breaking open after the patient is allowed up. In addition, it is important to ligate them before operating on the communicating veins, because if the incision for the latter should become infected, there is then no danger of septic emboli being cast off into the circulation from the saphenous veins, as occurred in one of the patients reported in this series.

The third step consists in an ambulatory period of about six weeks. The treatment during this time is directed toward keeping the ulcer healed until the skin of the lower leg is sufficiently clean to permit ligation of the communicating veins of the lower leg without danger of infection developing in the operative wound. Skin grafts will rapidly disintegrate and the ulcer will soon recur if some support is not furnished to the lower leg. Accordingly, it was found that an elastic adhesive bandage applied directly to the skin from the toes to just below the knee provided excellent support in most cases. If a patient is sensitive to the adhesive compound on the bandage, an Unna's paste boot is applied instead. These forms of support should be changed every two weeks. In most cases it is possible by this means to prevent the recurrence of the ulcer and to get the skin in a condition for operation on the communicating veins within six weeks from the time the patient was discharged from the hospital.

The fourth step consists in the ligation of the communicating veins of the lower leg. These are a series of vessels which connect the deep and the superficial systems of veins. The former are the posterior tibial, anterior tibial, peroneal, and popliteal veins, and the latter are the long and short saphenous veins. Under normal conditions the communicating veins have valves which allow the blood to pass only from the superficial system to the deep system. The communicating veins of the lower leg have been divided into three main groups; the medial, the anterior, and the lateral (Figs. 1, 2, and 3). This was done in order to facilitate their surgical exposure. The medial group is made up of the posterior tibial and the medial subdivision of the anterior tibial communicating veins. They connect chiefly with the long saphenous system, and are found on the medial side of the lower leg posterior to the inner edge of the tibia. The anterior group consists of the central and lateral subdivisions of the anterior tibial communicating veins. They lie on the anterolateral surface of the lower leg between the tibia and fibula. They also join tributaries of the long saphenous vein. The lateral group is made up of

there are six to eight veins in each group, so that there is a total of twenty to twenty-four of them. For a more detailed account of these veins reference should be made to a recent article by Linton.¹²

After the patient is admitted for the ligation of the communicating veins the skin is very thoroughly cleansed before performing the operation. Since fungus infection of the skin is practically always present

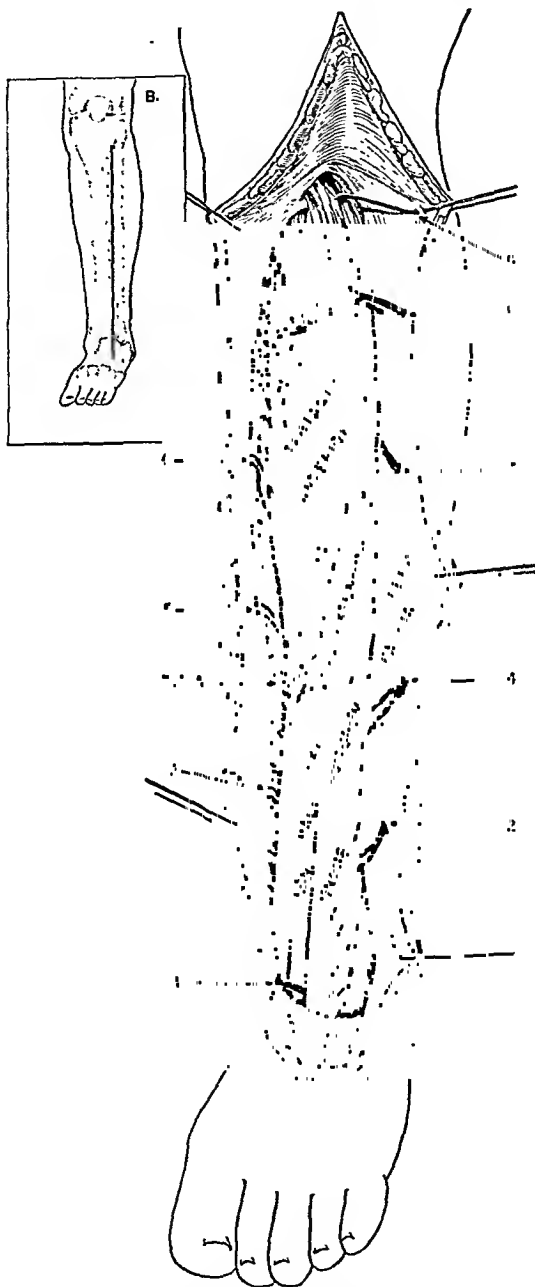


Fig. 2.—The anterior group of communicating veins of the lower leg. A dissection of the anterior aspect of the lower leg to show the anterior group of communicating veins beneath the deep fascia. No. 1, 2, 4, 7, 8, and 9 are the lateral subdivision of this group emerging along the anterior peroneal intermuscular septum. The tibialis anticus muscle is retracted laterally to show the veins of the central subdivision, No. 3, 5, and 6, on the lateral aspect of the tibia. The inset shows the location of the incision used in the operation for the ligation of these veins. (From Ann. Surg. April, 1938.)

about the old ulcer area, a fungicide is a great aid in cleaning it up.* One which has been found most efficacious consists of a 95 per cent ethyl alcohol solution containing 2 per cent resorcinol, benzoic acid, and boric acid. This is painted on once or twice a day after washing the leg with soap and water.

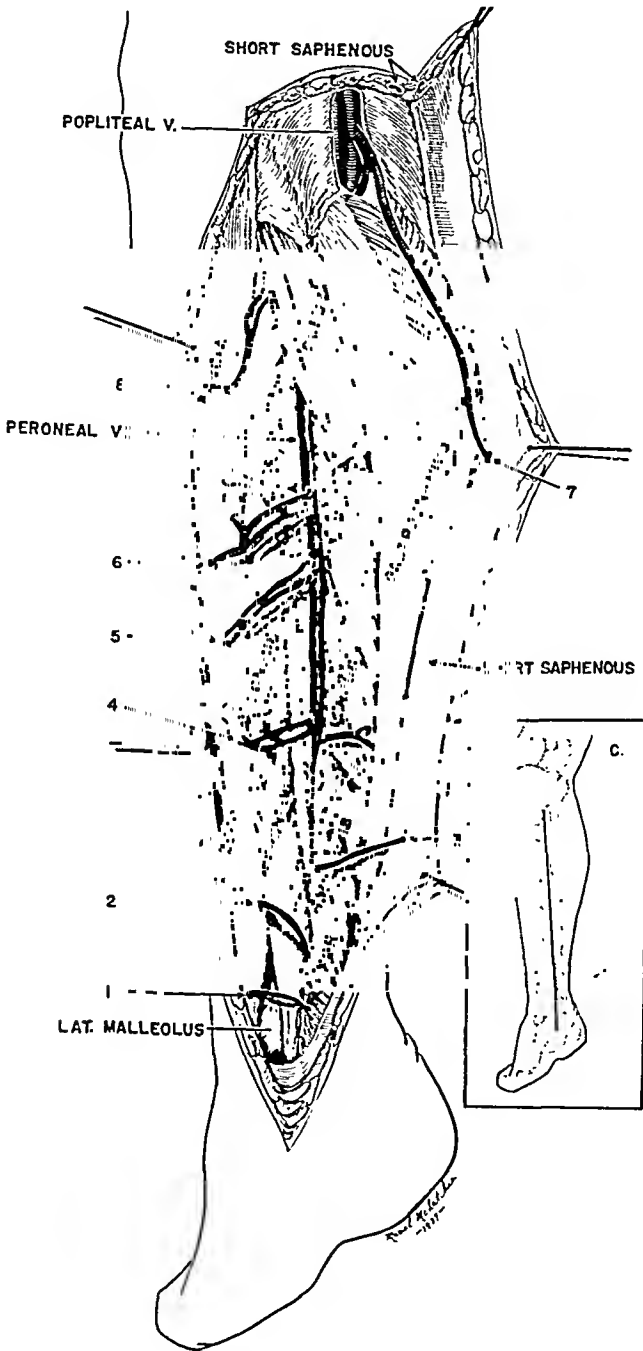


Fig. 3.—The lateral group of communicating veins. A dissection of the postero-lateral aspect of the lower leg to show the lateral communicating veins as they arise from the peroneal veins and pass outward along the posterior peroneal intermuscular septum. These are No. 1, 2, 3, 4, 5, 6, and 8. Posteriorly, the deep fascia has been elevated to show the popliteal communicating vein, No. 7. The short saphenous vein is shown superficial to the deep fascia. The inset shows the incision used in the operation for the ligation of these veins. (From Ann. Surg. April, 1938.)

*It is felt that fungus infection plays an important role in the etiology of varicose ulcers, and further work is in progress in an attempt to substantiate this view.

Ligation of the communicating veins is performed under spinal anesthesia. If the medial group is to be ligated the patient is placed in the Sims position with the affected extremity down. For the lateral group the patient lies face downward with the feet everted, and for the anterior group he lies on his back. The anatomic study of the veins revealed that they could all be readily exposed through three straight longitudinal incisions. The locations of these are shown in the insets of Figs. 1, 2, and 3. The use of straight incisions is especially emphasized. The incisions are carried through the deep fascia down to the muscles. The dissection is readily made between them and the deep fascia, as the only structures encountered are the communicating veins with small arteries accompanying them and a loose areolar connective tissue. They are divided and ligated beneath the deep fascia. The wound is carefully sutured with interrupted stitches in the fascia and the skin. Black silk (size No. 5) has been used in the majority of the cases in this series. The leg is placed in a posterior plaster shell from the toes to just below the knee. This immobilization aids primary healing. The dressing is done for the first time on the tenth postoperative day, when half of the skin stitches are removed. The remainder are taken out on the twelfth day. If the wound has healed per primam, postural leg exercises are commenced about the twelfth day to re-establish normal circulatory tone. These exercises are a modification of those described by Buerger¹³ and Allen,¹⁴ in that the period of elevation is longer than the period of dependency. They are done by elevating the legs to a thirty or forty degree angle with the horizontal for a period of three minutes. Then the lower legs are hung over the side of the bed for two minutes. This is followed by a five-minute rest with the legs in the horizontal position. The exercises are done in half-hour or hourly periods for a total of three or four hours a day. When the patient is allowed out of bed, the affected leg is bound firmly from the toes to the knee with an elastic adhesive bandage.

The fifth step in the cure of the ulceration consists in the postoperative care after the patient is discharged from the hospital. An elastic adhesive bandage or a paste boot is worn for a period of two to four weeks. Following this the patient should be instructed to wear an elastic stocking or a bender bandage for a period of several months to control the edema which is likely to develop. In addition, it has been found important that the patients bathe their legs and feet frequently with soap and warm water. After thoroughly drying the leg the ulcer area is painted with the fungicide that was used preoperatively. The purpose of this treatment is to eradicate the dermatitis, presumably of fungus origin, which so often persists following the operation. In some cases superficial ulcerations have developed postoperatively as a result of this dermatitis, but all of them have responded very rapidly to the above treatment.

Thirty cases of postphlebitic varicose ulcer in which the ulcer was treated by this method during 1937 at the Massachusetts General Hospital are reported in this paper. Twenty-three of the patients, or 77 per cent, were women, and seven, or 23 per cent, were men. The ages ranged from 22 to 66 years. Divided according to decades there were one in the third, ten in the fourth, nine in the fifth, seven in the sixth, and three in the seventh. These statistics point to the fact that this disease is much more common in women than in men and manifests itself chiefly in the middle age group, as 26, or 87 per cent, of the cases occurred between the ages of 30 and 60 years.

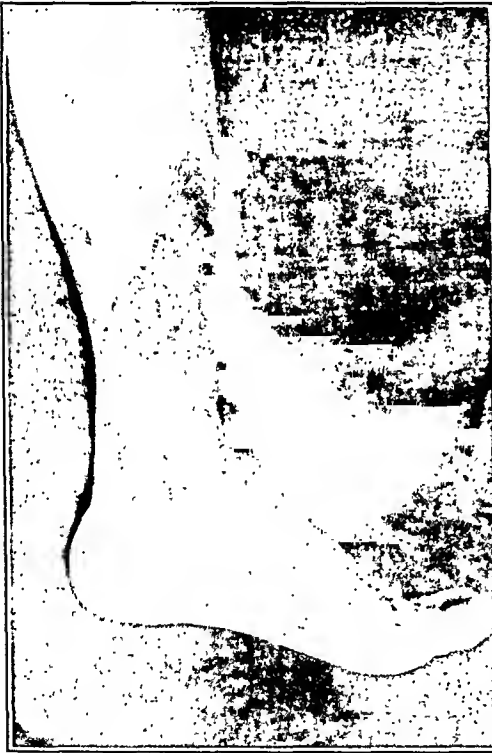


Fig. 4.



Fig. 5.

Fig. 4.—A photograph of the medial side of the left lower leg of a colored woman aged 58 years showing a postoperative phlebitic ulcer of twenty years' duration. This had been open intermittently and treated with salves and elastic bandages.

Fig. 5.—A photograph of the same leg taken May 7, 1938, ten months after the ligation of the communicating veins. There was very marked fibrosis of the subcutaneous tissues in the lower one-half of the leg. The line of the incision is seen in the upper portion of the leg and behind the malleolus. It has disappeared in the region of the old ulcer area. The patient wears a bandage part of the time. There is slight edema of the entire leg. The fungicide mentioned in the paper has been used two to three times a week. The ulcer has remained healed during this time and the result is to be classed as excellent.

A definite history of a preceding attack of deep thrombophlebitis was obtained from twenty-three patients. In two cases the history was questionable and in five it was not obtainable. In fourteen cases the phlebitis occurred post partum, in six it developed during the course of an infectious disease, in two it was postoperative in nature, and in one it followed trauma to the leg. The phlebitis occurred from five to forty years

prior to the admission to the hospital. A blood Hinton test for syphilis was reported on twenty-six of the cases, in only one of which was it positive.

There were forty-one ulcers present in this group of thirty patients. Thirty-two, or 78 per cent, were located on the medial side of the leg, six, or 15 per cent, were on the posterolateral surface, and three, or 7 per cent, were on the anterolateral aspect. In nineteen cases the ulcers had been present for one to ten years. Eight had been present for ten to twenty-five years. The longest duration was forty years, and there were only two that had been present for less than one year. In twenty-three



Fig. 6.—A close-up photograph of the ulcer area in the same patient taken ten months after the ligation of the communicating veins. The whitish tissue represents the area of marked subcutaneous fibrosis. The incision is visible in the upper and lower portions of the photograph but not in the central part. The two irregular dark areas in the center of the photograph are the skin grafts placed over the ulcers twelve months before this photograph was taken. This was very soft and pliable, excellent evidence that the fibrosis in the subcutaneous tissues is not the cause of these ulcerations.

cases the lesion was unilateral and in the remaining seven it was bilateral, making a total of thirty-seven extremities operated upon.

Forty-five operations were done on the communicating veins of the lower leg. Some patients had several ulcers on one leg, necessitating operating on two or more groups of communicating veins. One patient had all three groups of veins on each leg ligated because of ulcers over the internal and external malleoli of both legs. The operations and operative mortality following ligation of the communicating veins for

forty-one postphlebotic varicose ulcers were as follows: Thirty-five, or 78 per cent, were performed on the medial group of veins; seven, or 15 per cent, on the lateral group; and three, or 7 per cent, on the anterior group. It is interesting to note that in thirty-five extremities, or 95 per cent of the thirty-seven affected legs, the medial group were ligated, indicating that these veins are the ones which most commonly become incompetent. There was one death in this group of patients, a mortality rate of 2 per cent. It was directly attributable to sepsis in the operative wound. This resulted from inadequate preoperative preparation of the skin of the lower leg, as the communicating veins were operated upon twelve days after the ulcer was skin-grafted. The rule now is not to ligate these veins until six weeks after the ulcer has healed. Another lesson learned from this case was that the saphenous veins should be ligated before the communicating veins, because the death was due to septic emboli arising from the saphenous vein which had not been ligated. Since then this vein is tied off before the patient is discharged from the hospital the first time. The operative mortality based on the number of operations on the communicating veins was slightly over 2 per cent.

TABLE I

END RESULTS

POSTPHLEBITIC VARICOSE ULCERS (1937)
Thirty-five Extremities (Twenty-eight Patients)*

NO. EXTREMITIES	PER-CENTAGE	DURATION FOLLOW-UP	RECURRENCES	PER-CENTAGE
17	49	1-1½ yr.	1	6
7	20	9-12 mo.	0	0
10	28	6-9 mo.	0	0
1	3	5 mo.	0	0
			1	3

*One patient in the group of thirty died from postoperative infection and one other patient could not be traced.

Follow-up studies were made on twenty-eight of the twenty-nine patients who survived the operation (Table I). One patient could not be traced. In this group there were thirty-five extremities that were operated upon. In seventeen, or 49 per cent, the operation had been done one year, or more, before the follow-up examination; in seven, or 20 per cent, nine months, or more, before; in ten, or 28 per cent, six months, or more, before; and in one, or 3 per cent, five months before. Twenty-four patients were examined personally and the remaining four replied by letter to inquiries concerning their legs.

The results in all the cases except one were very satisfactory, as in only one case was there a recurrence of the ulceration. This was in a woman, operated on thirteen months previously, who suddenly developed, two weeks prior to the follow-up studies, an open lesion at the site of the old ulceration associated with an itchy vesicular rash. The original ulcer

had remained healed until that time. This result should not be classified as a failure, as the recurrent ulcer rapidly responded to ambulatory treatment with borie acid solution compresses and the fungicide mentioned above. In the remainder of the cases the results as far as the ulcerations were concerned could be classed as excellent. Thirty-nine ulcers, or 97.5 per cent of the forty that were present when the patients were first seen, were healed at the time of this follow-up study.

TABLE II
ANALYSIS OF END RESULTS

A. THIRTY-FIVE EXTREMITIES			B. FORTY ULCERS		
Elastic support all day	6	(17%)	Ulcers healed	39	(97.5%)
Elastic support part of day	7	(20%)	Ulcers not healed	1	(2.5%)
No support	19	(54%)			

In the majority of the patients the affected extremity, when only one was involved, still remained larger than the normal leg. This was due to varying amounts of a brawny type of edema, presumably the result of damage to the lymphatics at the time of the original deep thrombophlebitis. Bandages or elastic stockings were worn all day on six extremities, or 17 per cent, because of edema; on seven, or 20 per cent, they were only worn for varying periods during the day, for instance, for protection during working hours; on nineteen, or 54 per cent, no supporting bandages or stockings were worn. Information concerning the remaining extremities was not obtained.

DISCUSSION

The results obtained in the treatment of postphlebitic varicose ulcers by the method described indicate the importance of severing the communications between the deep and superficial veins when the valves in these communicating vessels are incompetent. It is worthy of note in these cases that it was necessary to inject very few of the superficial veins with a sclerosing solution following division of these vessels; in some cases no injections were needed. This indicates that the cure of the postphlebitic varicose ulcer depends in a great measure on preventing the hydrostatic pressure of the deep system of veins from being directly transmitted to the superficial veins.

The importance of the communicating (perforating) veins in the etiology of varicose ulcers has been recognized for many years. Homans,¹ in 1917, and Trout,² in 1929, stressed the role these vessels play in the etiology of the ulcer formation and recommended that they be ligated, but did not discuss the operative technique. In addition, an operation known as the "flap" operation for the ligation of the communicating (perforating) veins was done at the Massachusetts General Hospital for a number of years. The operation consisted in the raising of a flap of skin and fascia by means of a curved incision over the region where the

incompetent veins were present, or around a healed ulceration. The communicating veins were ligated beneath the deep fascia in the same way as is described in this paper. However, the operation fell into disrepute because (1) the curved incision not infrequently resulted in necrosis of the skin edge of the flap, which often required weeks or months to heal, and (2) the incision was usually a relatively short one so that the operation was frequently incomplete and recurrences resulted. Ligation of the communicating veins is therefore not an original or new operation. However, the entire operative procedure that is described in this paper for the treatment of postphlebitic varicose ulcers is original and is based on anatomic dissections.

The medial group of communicating veins was found most often to be incompetent. Of these the ones in the lower half of the leg were usually the most dilated. This apparently is because of the fact that the veins in this region pass out through tendinous structures which give little if any support to the veins, so that they may readily be stretched by increased venous pressure and so become incompetent. In the upper half of the leg they pass out between large muscle bellies which give them more adequate support. The anterior and lateral groups of communicating veins likewise have greater muscular support than the veins in the lower half of the inner side of the leg. These facts probably explain the greater frequency of medial ulceration—in this series 78 per cent.

In the postphlebitic leg with ulceration it is very difficult to palpate the communicating veins because of edema and fibrosis. However, the location of the ulcer indicates which group or groups of veins are incompetent. If the ulcer is situated on the medial or inner side of the leg it is the medial group of communicating veins that is incompetent; if it is on the anterolateral surface it is the anterior group, and if it is located on the posterior or posterolateral surface it is the lateral group. In some patients multiple ulcerations may be present so that two or more groups may be involved. An ulcer located over the anterior aspect of the tibia so that it extends on the anterolateral as well as the inner aspect of the leg usually indicates that the medial and anterior groups are incompetent. The long saphenous vein should be ligated at the saphenofemoral junction if the medial or anterior groups of communicating veins are to be ligated, and the short saphenous vein in the popliteal space if the lateral group is to be ligated.

The use of an efficient fungicide both in the preparation of the skin for operation and for use postoperatively is a very important adjunct to the surgical treatment that has been described.

CONCLUSIONS

1. A series of forty-one postphlebitic varicose ulcers in a group of thirty patients is reported.

2. A new method of treatment by ligation of the saphenous veins and the communicating veins of the lower leg is given.
3. Follow-up studies on these patients, made at intervals varying from five months to one and one-half years after treatment, are reported.
4. Thirty-nine, or 97.5 per cent, of the ulcerations were healed at the time of the follow-up study.

REFERENCES

1. Homans, J.: The Etiology and Treatment of Varicose Ulcers of the Leg, Surg., Gynec. & Obst. 24: 300, 1917.
2. Douglas, B.: Conservative and Radical Measures in the Treatment of Ulcer of the Leg, Surg., Gynec. & Obst. 61: 458, 1935.
3. Krinsky, C. M.: Treatment of Varicose Ulcer by Gentian Violet, New England J. Med. 211: 803, 1934.
4. Thurmon, F. M., and Chaimson, H.: Gentian Violet Treatment of Leg Ulcers, New England J. Med. 216: 11, 1937.
5. Edwards, E. A.: The Treatment of Recurrent Varicose Ulcers, New England J. Med. 212: 450, 1935.
6. Saylor, L., Kovacs, J., Duryee, A. W., and Wright, I.: The Treatment of Chronic Varicose Ulcers by Means of Acetyl-Beta-Methylcholine Chloride Iontophoresis, J. A. M. A. 107: 114, 1936.
7. Mayo, C.: Treatment of Varicose Veins. Surg., Gynec. & Obst. 2: 385, 1906.
8. Trout, H. H.: Ulcers Due to Varicose Veins and Lymphatic Blockage, Arch. Surg. 18: 2281, 1929.
9. Brown, J. B., Byars, L. T., and Blair, V. P.: A Study of Ulcerations of the Lower Extremity and Their Repair With Thick Split Skin Grafts, Surg., Gynec. & Obst. 63: 331, 1936.
10. Pennoyer, G. P.: The Treatment of Varicose Ulcers and Veins, Ann. Surg. 99: 997, 1934.
11. Douglas, B.: The Radical Repair of Large Skin Defects With Particular Reference to Leg Ulcers, South M. J. 24: 53, 1931.
12. Linton, R. R.: The Communicating Veins of the Lower Leg and the Operative Technic for Their Ligation, Ann. Surg. 107: 582, 1938.
13. Buerger, Leo: Circulatory Disturbances of the Extremities, Philadelphia, 1924, W. B. Saunders Company.
14. Allen, A. W.: Recent Advances in the Treatment of Circulatory Disturbances of the Extremities, Ann. Surg. 92: 931, 1930.

INTRACRANIAL VASCULAR LESIONS*

WINCHELL MCK. CRAIG, M.D.

ROCHESTER, MINN.

INTRACRANIAL vascular lesions comprise a very small but important group of lesions simulating tumor of the brain. They may be associated with vascular lesions elsewhere in the body; for example, thromboangiitis obliterans of the brain has been described as a clinical entity associated with generalized thromboangiitis obliterans. However, the intracranial vascular lesions which are not associated with vascular lesions elsewhere in the body create most of the difficulty in differential diagnosis.

At one time, it was thought that intracranial vascular lesions occur only among elderly people; however, congenital or developmental anomalies may occur among children and young adults. The blood vessels of the brain are subject to various types of malformation and anomalies from which symptoms may develop insidiously or suddenly. Rupture of a congenital aneurysm involving an artery leading into or arising from the circle of Willis may cause diffuse subarachnoid hemorrhage with sudden headache and collapse. The presence of such an aneurysm rarely is recognized until it has ruptured, although, once suspected, the diagnosis may be made before rupture occurs by means of roentgenograms of the head taken immediately after the injection of thorium dioxide (thorotrast) into the internal carotid artery. Arteriovenous aneurysms of the brain have been considered congenital in origin, although in other portions of the body such lesions are usually of traumatic origin. An arteriovenous aneurysm of the brain, according to Dandy,¹ consists of dilated arteries with an angiomatous formation interposed between the arterial supply and a tremendously dilated venous system into which arterial blood enters. Whereas it is true that some authorities state that arteriovenous aneurysms of the brain are always congenital, in a review of our cases it was found that in a certain number there was a definite history of injury preceding the development of symptoms. We may assume that in these cases there is an underlying congenital tendency, but the traumatic etiological factor must not be underestimated. To further this conception, Cushing and Bailey² quoted Schüek,³ who believed that whereas the vascular lesions may arise from a developmental fault, they are capable at a given time, owing to trauma or some other stimulus, of becoming active and producing symptoms.

*Read before the meeting of the American Heart Association, San Francisco, Calif., June 11, 1938.

Received for publication July 20, 1938.

Intraeranian vascular lesions have been divided into several classifications. Cushing and Bailey² seem to have divided them into the most simple and practical groups in their book "Blood Vessel Tumors of the Brain." These groups are telangiectasis, angioma venosum, arterial angioma or aneurysmal angioma. This classification includes only the vascular lesions over the surface of the brain. In addition to these, aneurysms of the carotids and anterior, middle, and posterior cerebral arteries produce symptoms of supratentorial tumor, and aneurysms of the vertebral, basilar, and cerebellar arteries simulate tumors of the cerebellopontine angle and cerebellum.

ANEURYSMAL ANGIOMAS

The presence of aneurysmal angioma may be suspected if a patient relates a long history of repeated convulsive seizures followed by temporary weakness or paralysis of one or more extremities. However, such a history also may be associated with tumors of the brain. Sometimes, roentgenologic examination of the head is of value and may give evidence of characteristic calcification in the walls of the abnormal blood vessels. Auscultation of the skull should be routine in the examination of all patients with intraeranian lesions because the bruit, of which the patient may be unaware, often is detected with the stethoscope. Although a bruit may indicate the presence of a vascular lesion, we have encountered a number of cases in which bruits have been associated with increased intraeranian pressure produced by a tumor of the brain.

The surgical treatment of aneurysmal angioma sometimes is followed by discouraging results. However, ligation of the artery with or without cauterization of the vein may relieve jacksonian convulsions, but there is always danger of producing permanent paralysis. Probably the most successful results are in cases in which the wormlike collection of vessels produces irritation of the cortex, and ligation and cauterization do not destroy the blood supply to the deep structures of the brain. Such a case was the following:

CASE 1.—A woman, aged 25 years, came to the clinic complaining of generalized convulsions, pain in the head, and visual difficulty. She had experienced occasional headaches for the previous four years, and sometimes she would become stuporous during the headaches and could be aroused only with difficulty. A generalized convulsion occurred the day before the delivery of her only child, one year before her examination at the clinic. The convulsion lasted a few minutes during which she bit her tongue. Following a normal delivery her general health was good until nine months later. While planting flowers in the garden she suddenly lost consciousness again and bit her tongue. She recovered and walked to the house following which she had a severe convulsion and was unconscious for four hours. One month previous to her registration at the clinic she had a sudden onset of sharp pain which was projected from the occiput around the base of the skull, was associated with vomiting for several hours, and was followed by unconsciousness lasting four or five days, for which she was hospitalized elsewhere. A week before her examination at the clinic she had an attack of numbness involving the entire left arm and hand which

lasted for several hours. She had experienced failure of vision for one month before examination at the clinic.

Neurological examination and roentgenologic examination of the head gave negative results. Examination of the eyes revealed a left homonymous upper quadrant hemianopsia. No bruit could be heard on auscultation of the head. Ventriculograms revealed a lesion in the right rolandic region. Craniotomy disclosed a normal appearing dura under increased tension, and when the dura was reflected a wormlike aneurysmal vascular lesion involving the sylvian and rolandic vessels was found (Fig. 1). The entire hemisphere pulsated. During the dissection of the dura from the arachnoid two large arteries were torn, necessitating ligation. Following recovery the patient was given one course of radiotherapy. Residual weakness of the left extremities did not occur. Four months following operation she had experi-

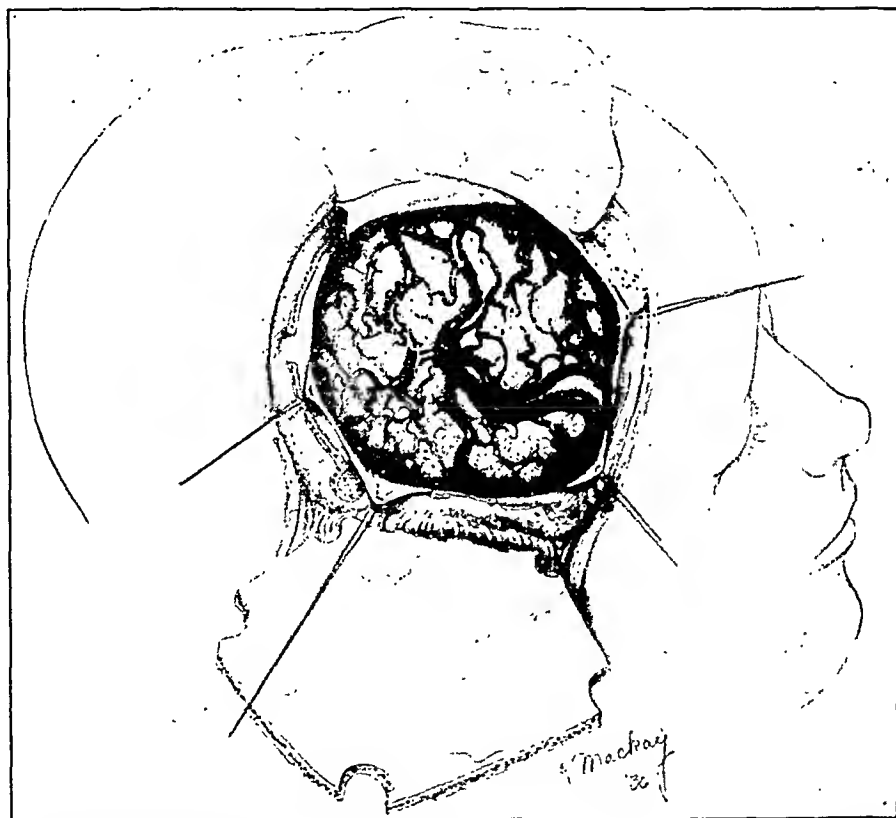


Fig. 1.—Aneurysmal vascular lesion producing convulsions, unconsciousness, and paresthesias.

enced neither headache nor attacks of jacksonian or generalized convulsions, although she was taking phenobarbital. Two years later, after a strenuous round of bridge and social activities, she had slight numbness of the left arm but otherwise had been perfectly well in the interval.

CASE 2.—A woman, aged 26 years, came to the clinic complaining of paresis of the left arm and generalized convulsions. At the age of 10 years she began having attacks of numbness and weakness of the left hand when she was under emotional excitement. At 18 years of age, one or two weeks before a menstrual period, she noticed a similar attack of numbness which lasted only a few moments. At the same time she began to have fainting spells. At the age of 22 years she was shocked by the death of her fiancé and, following this, she had spells of numbness of the left hand which became progressively more frequent and of longer duration.

After a sudden marriage and divorce she entered a nurses' training school and in the operating room became unconscious and had a generalized convulsion in which the left arm waved about and became spastic. She recovered in two or three minutes. After three such attacks she was sent home with a diagnosis of epilepsy. Following another convulsion she was sent to a hospital and after a week's observation she awoke at 3 o'clock one morning and noticed that her left arm was paralyzed. The paralysis disappeared in three hours. Later, the same morning, the arm became paralyzed again, and in addition she experienced numbness and weakness of the left leg. This disability persisted for four months, during which time there was slight recovery of motion of the hand and arm. During this time she had generalized and jacksonian convulsions every week or ten days.

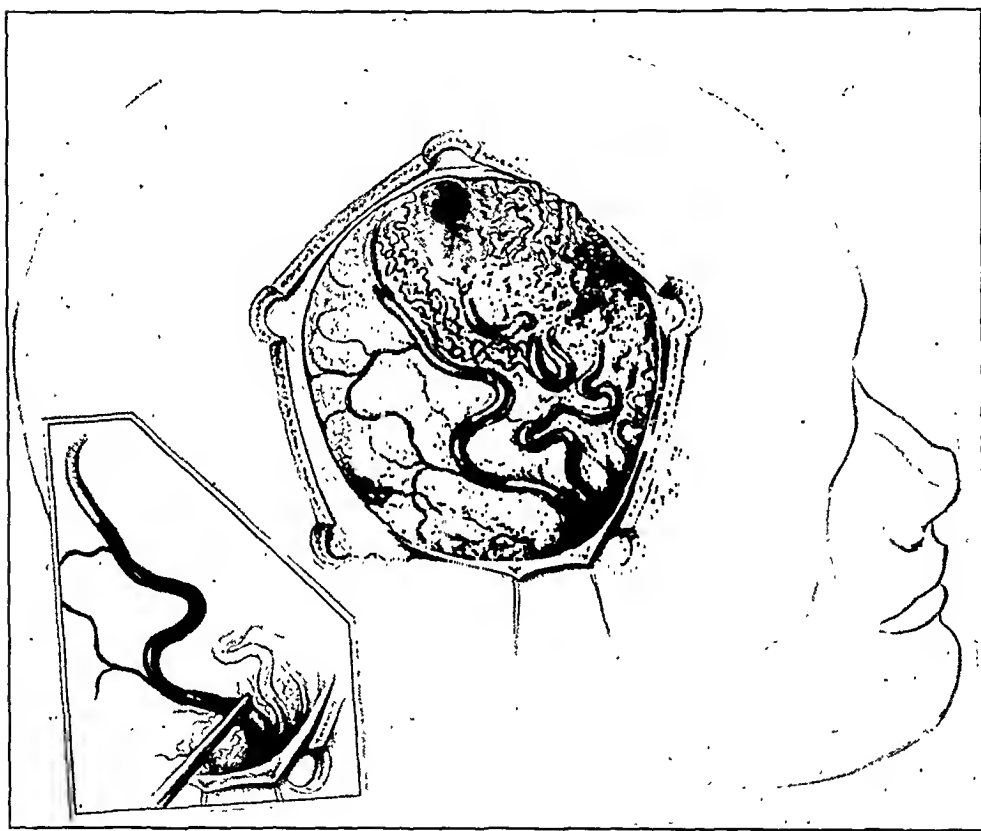


Fig. 2.—Aneurysmal angioma exposed at operation.

On general examination, considerable weakness, loss of tone and slowness of movement, and mild atrophy of the entire left upper extremity with an absence of reflexes were noted. Examination of the eyes and roentgenologic examination of the head gave negative results.

At operation, an aneurysmal angioma involving the right parietal region was found. Arterial blood could be seen coming from the middle cerebral artery, communicating through large vascular ramifications with communicating veins of the longitudinal sinus (Fig. 2). This mass measured about 7 cm. in diameter and 1 to 4 cm. in thickness. The entire parietal region of the brain had a bluish appearance and a definite arteriovenous lesion could be demonstrated by compressing the arterial branches of the middle cerebral artery. The larger arteries were ligated and the entire mass was coagulated, and as the coagulation of the vessels progressed there was definite shrinkage of the mass (Fig. 3).

Following operation, the sensation of the hand improved and she could move it more freely than before operation. She did not have difficulty in walking. A year later, although she was complaining of slight weakness in her left hand and arm, there had been neither grand mal seizures nor loss of consciousness, but there were occasional small convulsive seizures of the left hand. With the use of sedatives, phenobarbital, and bromides, she did not have further attacks.

Sometimes, merely decompression will help patients who have an aneurysmal varix, and it is very difficult at the time of operation to know when to employ conservative measures and when to be radical in treatment. A decompression followed by sedation may lead to gratifying results.

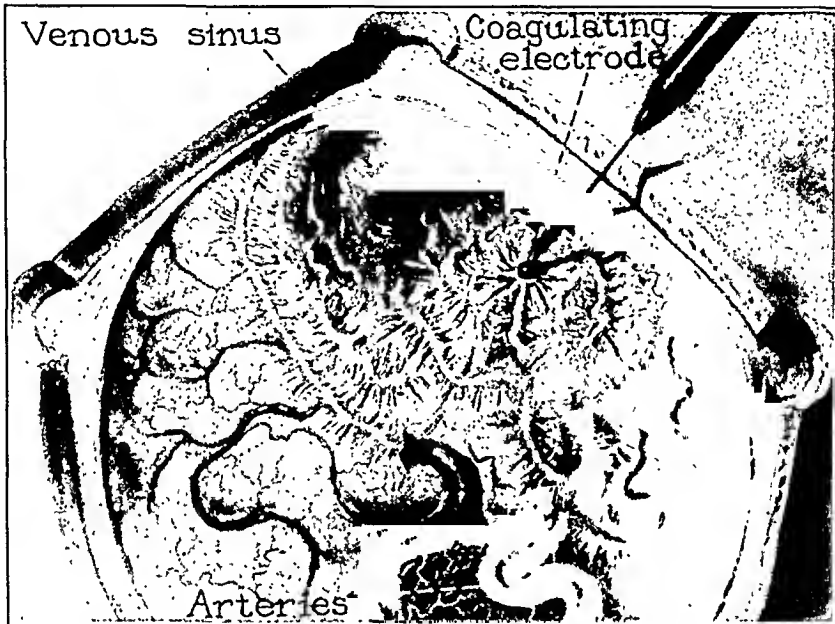


Fig. 3.—Aneurysmal angioma following ligation and coagulation.

CASE 3.—A man, aged 42 years, had been well until sixteen years before his examination at the clinic. While reaching for the telephone his right upper extremity became paralyzed, and this was associated with numbness and tingling. The paralysis gradually disappeared during the next three months, and except for an occasional transient attack of numbness of the right upper extremity, he was practically well for fourteen years. In the two years previous to registration at the clinic he had experienced an attack every week associated with minor cramplike contractions of the entire upper extremity. He had lost consciousness with about one-fourth of the attacks, which were initiated by cramping and drawing of the right hand and arm.

On examination it was found that 50 per cent of the strength in the entire upper extremity had been lost and that the reflexes were hyperactive. Craniotomy revealed a varicosity of the vessels, particularly the arteries, over the cortical region of the left hemisphere, involving particularly the arm center (Fig. 4). The vessels were greatly enlarged and were increased in number. Ligation and coagulation were not done, but a decompression was performed at the base of the flap. The patient returned home and was instructed to take a sedative, luminal. Two years later he was still having slight jacksonian convulsions involving the upper extremity about every month, but had not experienced generalized convulsions or attacks of numbness since the operation.

Sometimes there is definite evidence of trauma preceeding the development of symptoms of intracranial lesions, and if an aneurysmal angioma is found at the time of operation, trauma must be considered one of the etiological factors. In some of these cases it is also possible to perform a palliative operation, ligating some vessels and coagulating others to reduce the severity of the attacks and make the patient more comfortable. However, if the lesion involves the motor or speech area it is sometimes better to withhold further surgical treatment.

CASE 4.—A man, aged 49 years, came to the clinic complaining of jacksonian convulsions involving the entire right side of the body. In the spring of 1918 he had struck his head against a dugout timber, the point of contact being the left parietal region. He was unconscious for a few moments, and vomited; he had headaches for twenty-four hours. Following this he returned to duty. Three years later the



Fig. 4.—Cortical aneurysmal varix.

right arm and leg became very tired on exertion. Seven years after the accident he noticed weakness of the right arm and leg which disappeared in a few days. The first convulsion occurred nine years after the accident. When examined six weeks after the first convulsion he complained of repeated twitching of the right side of the face followed by loss of consciousness. He was very confused on recovery. He was given phenobarbital for one year, during which time he had three attacks, two very slight and one severe, in which jacksonian convulsions of the right side of the face and body occurred and were followed by loss of consciousness. Subsequently, he had sixteen attacks; thirteen were jacksonian in type, involving the right side, and in three loss of consciousness occurred.

On examination, slight residual weakness of the right arm and leg were found. Roentgenologic examination of the head and examination of the eyes gave negative results. There was a diminution of reflexes of the right extremities and slight tenderness over the left parietal region of the head. The involvement predominantly of the right side indicated that the lesion was in the left hemisphere. The left parietal lobe was exposed at operation. The brain was under moderate tension and the precentral convolution in its midportion was covered by a mass of arteries

which were poorly defined but had the appearance of an angle worm 3 cm. in diameter. From the central portion of this mass the dilated vessels radiated and appeared to communicate directly with the branches from the middle cerebral artery. These vessels varied in size from 0.5 mm. to 3 or 4 mm. The normal arteries, which usually have the appearance of capillaries, were dilated and seemed to form this angiomatic mass. There was definite pulsation synchronous with the pulse. The situation of the mass in the left cerebral hemisphere and the slight degree of motor

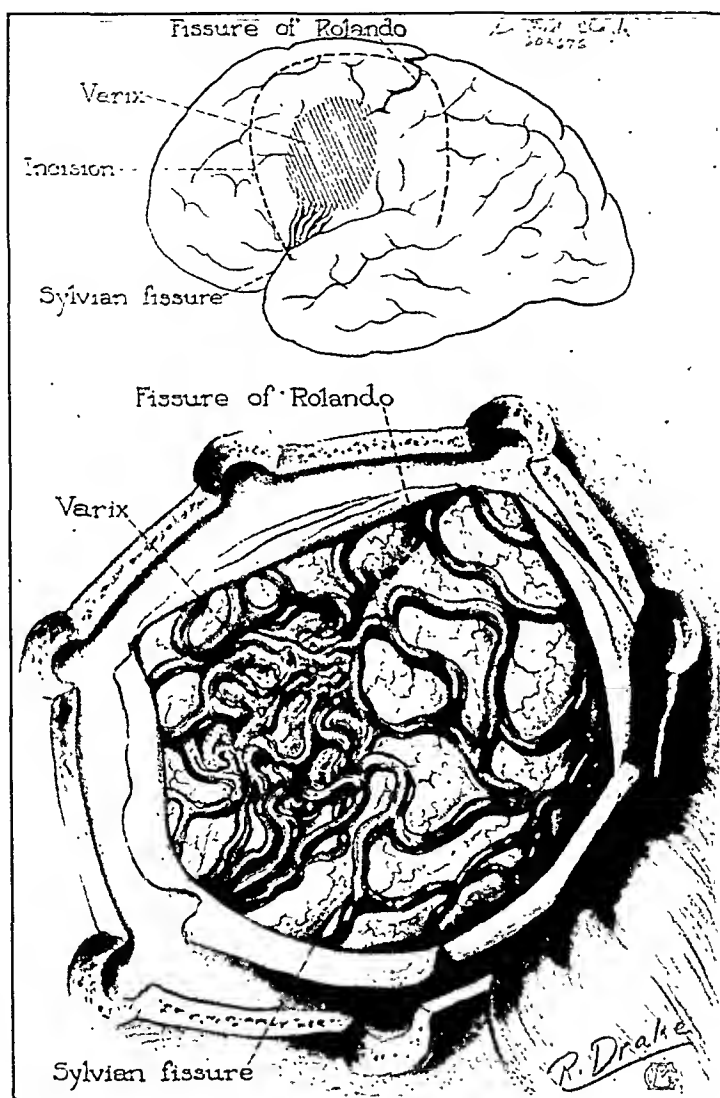


Fig. 5.—Aneurysmal angioma.

weakness on the right side contraindicated any radical surgical treatment (Fig. 5). Two days after operation the patient had a generalized convulsion. He was given phenobarbital for sedation, and four weeks after operation a very slight seizure involved the tongue. An intensive course of deep roentgenotherapy was given. He was examined four years after operation, with negative results. During the time that he had been taking three grains of luminal a day, he had been having about one attack in two months, consisting of twitching of the tongue with slight drawing of the right side of the face. Loss of consciousness had not occurred with any attack.

INTRACRANIAL ANEURYSMS

Intraeranian aneurysms may be elassed as arteriovenous or saccular in type. Saceular aneurysms may occur in any of the eerebral vessels and are most frequent in the region of the circle of Willis (Fig. 6). Saceular aneurysms of the intracranial portion of the internal carotid artery may be associated with different elinical pictures, depending on their size and situation. Supraclinoid aneurysms may simulate basofrontal tumors, with ehanges in the visual fields owing to pressure on the optie nerves or chiasm, anosmia, and mental aberration. By extension posteriorly they

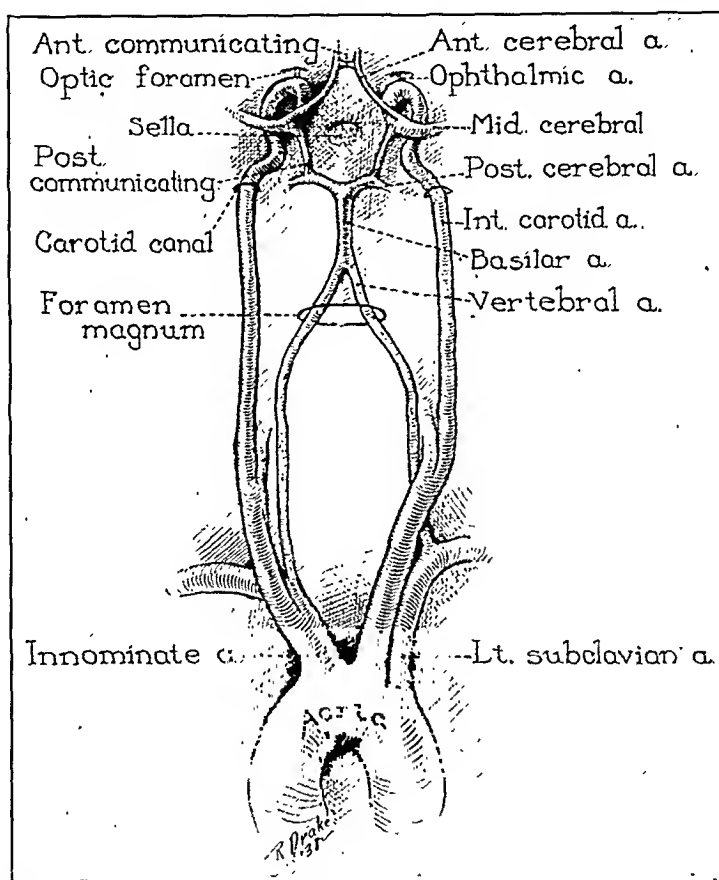


Fig. 6.—Sources of intracranial vascular supply with the relation of the vessels of the circle of Willis.

may press on the third nerve and cause ophthalmoplegia. Saccular aneurysms of the internal carotid artery within the sella are associated with a characteristic clinical picture, of which palsy of the third nerve, or ophthalmoplegia, is a most important localizing sign. Paralysis of the ocular muscles supplied by the fourth and sixth nerves also may occur, and pain in the region of the forehead and eye on the same side may be present because of the pressure on the ophthalmic division of the fifth, or trigeminal nerve. Pain in the cheek or jaw on the same side occurs occasionally because of pressure on the other divisions of the fifth nerve,

Intracranial aneurysms, besides producing pressure on contiguous brain and nerves, also may rupture, causing leakage of blood into the subarachnoid space, producing the well-known syndrome of spontaneous subarachnoid hemorrhage characterized by headache, vomiting, drowsiness and coma, associated with a bloody spinal fluid. Death frequently ensues. The diagnosis of intracranial aneurysm of the carotid artery is not difficult to make if the condition is kept in mind. Parker⁴ pointed out that it is only in cases of aneurysm associated with intermittent leakage and focal compression that correct localization of the aneurysm is possible. A bruit, frequently associated with arteriovenous aneurysms, is rarely heard in cases of saccular aneurysm. The results of roentgenologic examination of the skull are often negative, but calcification of the wall of the aneurysm, unilateral erosion of the sella turcica, enlargement of the sella, unilateral enlargement of the optic foramen and the superior orbital fissure, erosion of the margin of the carotid canal, and displacement of the pineal body have been observed. Intracranial arteriography following injection of thorotrast into the carotid artery has proved of value in the diagnosis in some cases of intracranial carotid aneurysm. A negative result from arteriographic examination, as has been pointed out by Sjöqvist,⁵ does not exclude the presence of an aneurysm, because thrombosis may occur in the aneurysm and fill the lumen.

In contrast with aneurysmal angioma, as regards etiology, it seems to be the consensus that most intracranial aneurysms are congenital, the aneurysmal path occurring on one or the other carotids or vessels comprising the circle of Willis. Tuffnell,⁶ in 1853, drew attention to the probability that embolism was the starting point of cerebral aneurysm. Lebert,⁷ in 1866, expressed the opinion that syphilis and the use of alcohol were not definite causes of this lesion, as had been supposed previously. Eppinger,⁸ in 1887, first proposed that intracranial aneurysms arose as a result of a congenital defect in the muscular wall of the artery. Weber and Bode⁹ suggested that the tendency of congenital defects to occur together was also a factor in the frequency of aneurysms in association with coarctation of the aorta.

The predilection of intracranial aneurysms for vessels in the base of the brain shortly after they enter the cranial cavity or at the point of bifurcation is constant. Most authors state that the middle cerebral artery is most frequently involved and that the basilar artery is next in order of frequency. In reviewing a total of 596 cases of aneurysm observed at the Mayo Clinic in the years 1925 to 1935 inclusive, Mills and Horton¹⁰ found that 143 of the aneurysms were intracranial, 339 were intrathoracic, eighty were intra-abdominal, twenty-one involved the extremities, and thirteen were of a miscellaneous character. Syphilis was present in 3.5 per cent of the cases of intracranial aneurysm (which is

the normal incidence), in 70 per cent of the cases of thoracic aneurysm, in 8.8 per cent of the cases of intra-abdominal aneurysm, and in 9.5 per cent of the cases of aneurysm of the extremities.

Our usual impression of intracranial aneurysm is that the patient is perfectly well until the occurrence of headaches, sudden in onset and prostrating in character. These headaches probably are associated with a sinking spell from which he recovers, only to have a second and third attack. Illustrative of such a condition is the following case:

CASE 5.—A man, aged 52 years, came to the clinic complaining of headache, bitemporal in situation and severe in character. He had suffered from "stomach trouble" with epigastric pain, nausea, vomiting, and headaches for the previous three years. During these attacks he had sinking spells with exhaustion, followed by unconsciousness which continued for a period of several hours. In one of these attacks he was hurried to the hospital, where he complained of diplopia and headache; he vomited before he lapsed into unconsciousness.

Spinal puncture revealed the presence of bloody fluid; following spinal drainage he seemed to be slightly better. However, he had another attack the following day, and on the fourth day had a severe attack from which he did not recover. At necropsy an aneurysm of the right middle cerebral artery was found, together with evidence of multiple rupture and basal hemorrhages which accounted for his condition.

In selected cases, intracranial aneurysm is treated by ligation of the homolateral carotid artery in the neck. Ordinarily, ligation is considered only when the individual is less than 40 years of age. The patient must be able to withstand digital compression of the homolateral carotid artery for thirty minutes without the development of alarming symptoms and signs, thus demonstrating the presence of an adequate collateral circulation through the circle of Willis. Digital pressure can be applied by the patient, in the beginning, for five minutes three times a day, and gradually increased to two hours, three times a day. It must be emphasized that correct diagnosis, localization, and proper surgical treatment are fully as important in cases of intracranial aneurysm as in those of brain tumor.

Walsh and Love¹¹ recently have reported a case in which ligation of the carotid artery was performed. The patient was an automobile mechanic, aged 39 years, who, fifteen years previously, had noted attacks of mild headache and dizziness while at work. These attacks were intermittent, and four years after the initial attack, while at work, the patient suddenly became unconscious and remained so for several minutes. Ten years later while pumping up a tire he experienced a sudden, severe pain in the cervical region; this pain extended to the top of his head. His neck became rigid and moving his head caused severe pain. About forty-five minutes later he had a chill, his temperature was elevated, and he vomited. The headache persisted for about two weeks. This was fol-

lowed by blurring of vision and inconstant diplopia; the headaches became more severe. Constant ptosis of the right eyelid occurred.

The pupil of the right eye was dilated and fixed. The right eyeball had rotated downward and outward; it could not be elevated. Internal rotations were greatly limited, indicating the presence of a complete palsy of the third nerve. Otherwise, the examination gave negative results and no bruit was audible over the head. A diagnosis of intracranial, infraclinoid aneurysm of the right internal carotid artery was made.

It was found that digital pressure on the right carotid artery in the neck could be made for thirty minutes without producing abnormal symptoms and signs. Ligation of the right internal carotid artery in the neck was carried out, as well as ligation of the right internal and external jugular veins. After ligation of the carotid artery the patient stated that the headache, which had been one of his chief complaints, had ceased. The internal jugular vein was also ligated. Following operation, the patient was entirely relieved of his headaches and the function of the third nerve on the right side returned.

Because we are inclined to think of vascular intracranial lesions which simulate brain tumors as occurring in elderly people, the following case is reported. There are several factors about this case that are of interest. In the first place, the patient was a girl aged 20 years; in the second place, symptoms occurred following a serious automobile accident, and in the third place, the history simulated very closely that of onset of symptoms associated with tumor of the brain. To illustrate further how it simulated tumor of the brain, evidence of calcification was found on roentgenologic examination of the head; the shadow of calcification was irregular in outline, was not typical of a vascular lesion, and could have represented either tumor or an old hemorrhage. However, a loud, constant bruit could be heard over the entire right side of the head.

CASE 6.—A girl, aged 20 years, was brought to the clinic with the complaint of headache, mental sluggishness, and general malaise. Two years previously she had been in a serious automobile accident and had sustained a contusion on the right side of the head, but she did not lose consciousness. She returned to school the next day and remained well until six months later when, suddenly, she had a generalized convulsion, following which she had severe headache in the right temporal region. About ten days later she had another convulsion without aura. The headaches continued intermittently without convulsions until one year later, when she had another convulsion, following which she remained in bed for about a week, during which time she experienced a moderate degree of numbness and weakness of the entire left side of the body, including the face. Following this episode, the family noted a mental change. The patient appeared less alert than usual, was apprehensive, and sometimes slightly confused. She also observed a slight momentary taste aura, the character of which was not clear. Three months later, with the onset of one of the severe headaches, she vomited, was dizzy, and for the first time noted diplopia, which persisted. Following this, the headache was more persistent. She observed some hallucinations in the left field of vision, but was unable to describe them. About this time she became aware of a rushing sound in her head.

The patient was rather dull and cooperated poorly. The sense of smell was severely impaired on the right side. There was weakness of the sixth nerve on both sides. The movements of the body on the left side were somewhat slow and clumsy; the deep reflexes were hyperactive. The plantar responses were normal. On examination of the fundi, bilateral swelling of five diopters was found; the fields were normal. Roentgenologic examination of the head disclosed evidence of irregular areas of calcification in the right frontotemporal region. A loud, constant bruit, which could not be obliterated by pressure on either carotid artery, was heard over the entire right side of the head.

Through a right frontal exploration, large tortuous vessels were encountered extending down into the sylvian fissure. Following the operation there was increased weakness of the left arm and leg and left side of the face. This improved, and on the sixth day, while the patient was sitting up, a series of convulsions suddenly developed, following which she died.

The brain was found attached to the dura in the right middle cranial fossa, and the attachment proved to be the extremely dilated petrosquamous sinus (which normally is a very small sinus draining into the lateral sinus). It was greatly distended and emptied into the lateral sinus through an opening which was much narrower than the other portions of the cavity. The anterior end of the sinus emerged from a large, firm, rounded, nodular aneurysm which could be seen on separating the temporal and frontal lobes. The right middle cerebral artery extended laterally and curved around the posterior aspect of the aneurysm in the sylvian fissure. About 4 cm. from its origin it was in close contact with the mass, and when the artery was opened its lumen was found to communicate freely with the cavity of the aneurysm. The sylvian vein was also very much dilated and emerged from the upper surface of the same pouch of the aneurysm which was drained by the petrosquamous sinus.

It is difficult to make a preoperative diagnosis of an intrasellar aneurysm that produces the signs and symptoms of a basofrontal, intrasellar, or extrasellar tumor; only at operation can the diagnosis be made. Even then, the gross appearance is deceiving and it is necessary to insert a small needle into the mass.

CASE 7.—A man, aged 39 years, came to the clinic complaining of failure of vision. Two years previously double vision developed, and suddenly he lost the vision in the right eye. Vision returned in one month and seemed normal for six months. At that time he noted bilateral visual impairment which gradually increased during eighteen months until, five days before his examination at the clinic, his vision failed completely.

Neurological examination gave essentially negative results except for complete loss of vision in the right eye; perception of light was present in the temporal portion of the left field. The ocular reflexes were abolished and there was a bilateral choked disk with secondary optic atrophy; the choked disk measured three diopters in the right and four diopters in the left eye. Several small hemorrhages were seen in each retina. The defect in the field of vision suggested a previous right homonymous hemianopsia. Roentgenologic examination of the head revealed severe destruction of the sella turcica and posterior clinoids and, from study of the roentgenograms, a diagnosis of intrasellar tumor with suprasellar extension was made. A right transfrontal craniotomy was done. The brain pulsated normally and was under normal tension, which was out of proportion to the degree of papilledema present. The right frontal lobe was elevated easily and evidence of tumor in the

right basofrontal region could not be found. The optic chiasm was exposed easily and was presenting anteriorly, but remaining within the sella was a bluish pulsating mass which could be compressed when touched with forceps. This mass also could be seen lying lateral to the optic chiasm and extending posteriorly (Fig. 7).

A diagnosis of intrasellar aneurysm was made which explained the visual symptoms as well as the evidence of erosion observed in the roentgenogram of the head. The optic nerves were smaller than normal and examination revealed evidence of pressure atrophy. The patient did not receive benefit from the operation.

Intracranial aneurysms may simulate any other type of lesion clinically, and frequently it is difficult to distinguish them by roentgenologic studies. Intracerebral calcification may be associated with gliomas, hemorrhage, and dermoid cysts, as well as with an aneurysm. Sometimes it is necessary to explore the lesion to determine its pathologic nature.

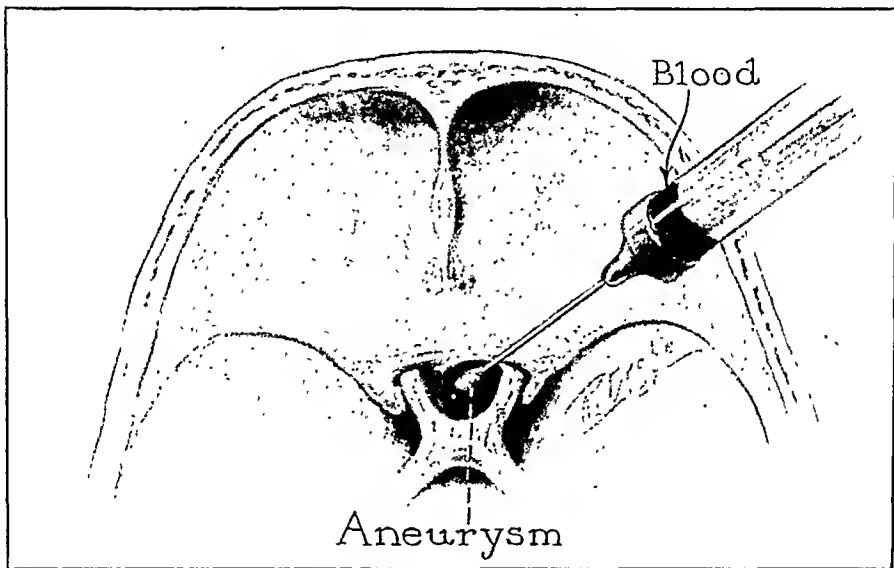


Fig. 7.—Intrasellar aneurysm simulating pituitary tumor.

CASE 8.—A man, aged 39 years, came to the clinic complaining of headaches and generalized convulsions which had occurred every four weeks for a period of thirteen or fourteen years, a constant pain behind the right orbit, blurring of vision, and weakness of the left side of the body. The headaches occurred almost every day, usually in the morning, beginning in the occipital region and extending over the entire head. The generalized convulsions usually began in the morning between 3 and 6 o'clock.

Neurological examination, including examination of the eyes, was entirely negative except for some slight weakness of both the left arm and left leg. Roentgenologic examination of the head revealed a large, calcified, cystic tumor above and behind the sella on the right side (Fig. 8). Because of the long history of slight weakness on the left side and the calcified lesion in the right middle fossa, it was thought wise to perform an exploratory operation. From the nature of the calcified shadow it was thought that either a calcified hematoma or a dermoid cyst would be found in the right temporal lobe. At operation, an incision was made in the superior temporal convolution, and at a depth of 2 cm. a large, calcified cyst wall was encountered. This was opened and was found to be filled with degenerat-

ing blood clot; this was removed completely. The thin, calcified wall could be resected easily from the surrounding brain by blunt dissection. The posterior half of the wall of the cyst was removed completely, but when the anterior wall was manipulated there was a sudden hemorrhage. This was controlled with packs, and the wound was closed. The patient died suddenly three days later. A large sacculated aneurysm of the right middle cerebral artery was found. Almost all of its calcified wall had been removed and the hemorrhage had occurred from a small opening between the artery and the calcified sac.

Intracranial aneurysms of the posterior fossa can simulate cerebellar tumors and lesions of the cerebellopontine angles, affecting the cranial nerves and compressing the contiguous pons and brain. Difficult to diagnose and distinguish from one another clinically, most of these lesions are identified at operation.



Fig. 8.—Calcified intracranial aneurysm of the right temporal lobe; A, anteroposterior view, and B, lateral view.

CASE 9.—A man, aged 37 years, came to the clinic complaining of weakness of the right side of the face and pain in the right eye. He was unaware of any weakness of the face until, eighteen months before he registered at the clinic, his children noticed that he slept with the right eye open. Shortly after this he was aware of the weakness of the right side of the face and it was diagnosed as Bell's palsy. One month before his examination he began to have occasional sharp pains in the right eye in addition to smarting or pain in the cornea. Examination, aside from the palsy of the seventh nerve and diminution of hearing on the right side, gave essentially negative results. Roentgenologic examination of the skull revealed an irregular erosion of the petrous portion of the right temporal bone mesial to the labyrinth and semicircular canal which appeared to be caused by a contiguous tumor. Because of the facial palsy and erosion of the contiguous bone, a unilateral suboccipital craniotomy was done and the right cerebellar lobe was elevated, allowing an excellent exposure of the cerebellopontine angle. Between the fifth and seventh nerves a large pulsating vessel, dark in color, could be seen compressing

both the seventh and eighth nerves and eroding the bone (Fig. 9). Evidence of tumor either of the cranial nerves or in this region could not be found. Following operation the patient did not improve clinically and was advised to have an anastomosis performed between the facial and spinal accessory nerves.

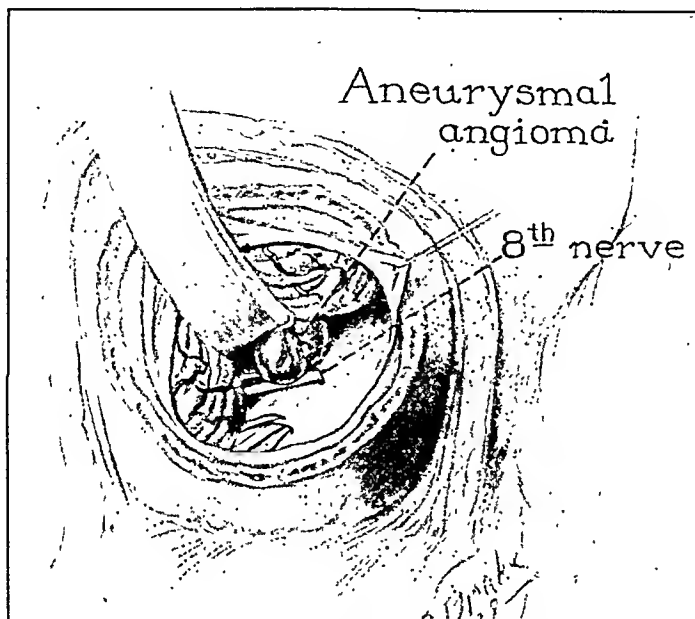


Fig. 9.—Aneurysmal angioma in the right cerebellopontine angle simulating tumor of acoustic nerve.

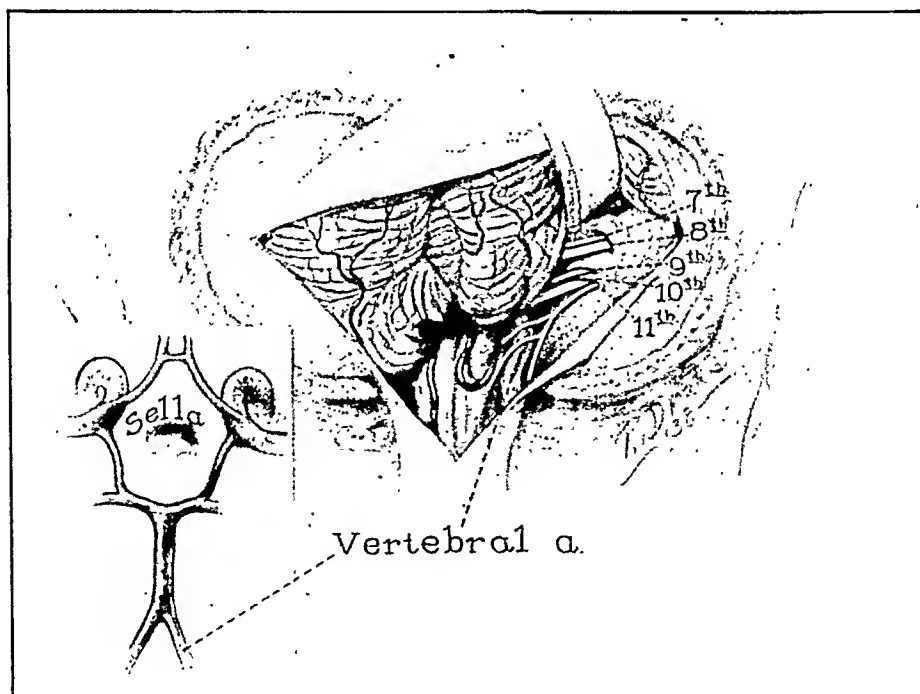


Fig. 10.—Aneurysm of the right vertebral artery simulating tumor of the right cerebellopontine angle.

A vascular lesion of the cerebellopontine angle, more extensive than that found in Case 9 and more closely simulating a tumor, was found in Case 10.

CASE 10.—A woman, aged 40 years, came to the clinic complaining of pain in the back of the neck, dizziness, staggering gait, and loss of hearing on the right side. Three and a half years previously, while suffering from a cold, she noticed that the hearing on the right was impaired. This had gradually become progressively worse. At about the same time, intermittent attacks of double vision began, associated with cramplike pains in the neck. Six months after the onset of the difficulty in hearing she began having a staggering gait. During the preceding year all the above symptoms were aggravated, particularly the staggering gait. The deafness progressed until the hearing was almost completely lost on the right side.

Examination of her eyes revealed slight diminution of vision in the right with normal vision in the left. Vertical nystagmus was noted. Papilledema and changes in the fields of vision were not found. Complete deafness of the right ear was present. The patient had such a severe degree of ataxia on the right that it was necessary for her to go about in a wheel chair. She held her neck stiffly and supported her head when sitting up or lying down. No bruit could be heard. The severe degree of ataxia on the right was associated with incoordination. A right suboccipital craniotomy was performed. Evidence of a tumor or an inflammatory lesion could not be found, but a large pulsating vessel could be seen compressing the pons, cerebellum, and cranial nerves. This vessel was an aneurysm of the right vertebral artery (Fig. 10). Associated with the aneurysm, the mesial surface of the cerebellum and pons was covered with a mass of telangiectatic vessels which involved the eighth, ninth, tenth, and eleventh nerves; this may have accounted for the patient's disability. Following her operation the patient had some temporary difficulty in swallowing and had to be fed through a tube. However, at the time of her dismissal her general condition was about the same as it was before operation.

COMMENT

Intracranial vascular lesions, although rare, so closely simulate tumor of the brain that a differential diagnosis is made with difficulty. Auscultation of the skull should be performed in every case of an intracranial lesion; if bruits are present, they usually signify the presence of a vascular lesion, although they may occur in association with tumors.

Aneurysmal angiomas must be treated conservatively, although it is sometimes necessary to ligate and cauterize the vessels. An intracranial aneurysm sometimes can be relieved, if the patient is young, by ligation of the carotid arteries, but digital compression should be performed first to determine whether or not untoward symptoms will develop from such a procedure.

Intracranial aneurysms can simulate cerebellar as well as cerebral tumors.

REFERENCES

1. Dandy, W. E.: *The Brain: Arteriovenous Aneurysms*. From Lewis and Dean's "Practice of Surgery," Vol. 12, p. 426, Hagerstown, Md., 1932, W. F. Prior Company.
2. Cushing, Harvey, and Bailey, Percival: *Tumors Arising From the Blood-Vessels of the Brain*, Springfield, Ill., 1928, Charles C. Thomas, Publisher.
3. Schüick: Quoted by Cushing and Bailey: *Ueber das Wesen und Entstehung der Angiom arteriale racemosum*. (Inaug.-Diss.), p. 9, Berlin, 1895.
4. Parker, H. L.: *Aneurysms of Cerebral Vessels: Clinical Manifestations and Pathology*, Arch. Neurol. & Psychiat. 16: 728, 1926.

5. Sjöqvist, Olof: Über intrakranielle Aneurysmen der Arteria carotis und deren Beziehung zur ophthalmoplegischen Migräne, *Nervenarzt* 9: 233, 1936.
6. Tuffnell: Quoted by Holmes, T.: Aneurism of the Internal Carotid Artery in the Cavernous Sinus, *Tr. Path. Soc.* 12: 61, 1860-1861.
7. Lebert, H.: Ueber die Aneurysmen der Hirnarterien, *Berl. klin. Wchnschr.* 3: 209, 229, 249, 281, 336, 345, 386, 402, 1866.
8. Eppinger, Hans: Pathogenesis (Histogenesis und Aetiologie) der Aneurysmen einschliesslich des Aneurysma equi verminosum, *Arch. f. klin. Chir.* (Supplement 1) 35: 563, 1887.
9. Weber, F. P., and Bode, O. B.: Congenital and Developmental Aneurysms and Their Importance in Regard to the Occurrence of Sudden Intracranial (Especially Subarachnoid) Haemorrhage, *Internat. Clin.* 2: 1, 1929.
10. Mills, J. H., and Horton, B. T.: Clinical Aspects of Aneurysm, *Arch. Int. Med.* (In press).
11. Walsh, M. N., and Love, J. C.: Intracranial Carotid Aneurysm: Successful Surgical Treatment, *Proc. Staff Meet., Mayo Clin.* 12: 81, 1937.

THE EFFECT OF MEDIASTINAL LESIONS ON PRESSURES IN THE ANTECUBITAL AND FEMORAL VEINS

REPORT OF FIFTY-TWO CASES*

HUGH HUDSON HUSSEY, M.D.
WASHINGTON, D. C.

A NUMBER of investigators have called attention to the fact that comparisons of the blood pressures in the veins of the four extremities have considerable significance in the localization and diagnosis of diseases causing compression of the venae cavae or their branches. Among the most interesting of such conditions are those in which lesions of the mediastinum cause differences in venous pressures in the two arms or in the arms and legs. The close relationship of the superior vena cava to the ascending aorta and to the hilar region of the right lung explains the frequency with which aortic aneurysm and tumors of the right hilar region cause compression of the superior vena cava without affecting the inferior vena cava (Fig. 1). Similarly, the left innominate vein is easily encroached upon by aneurysm, and both innominate veins are susceptible of involvement in cases of tumors or other lesions in the superior mediastinum.

Middleton¹ reports a case of aneurysm of the aorta in which the venous pressure in the left hand was about twice as high as in the right hand, presumably because of obstruction to venous return. Villaret, Saint Girons, and Grellety Bosviel,² in their summary of the subject of localized venous hypertension, cite several cases in which the effect of mediastinal lesions upon venous pressure measurements is exemplified. In one case of aortic aneurysm the venous pressure in the left arm was 150 mm. of water higher than in the right arm, indicating compression of the left innominate vein. In 5 other cases of aneurysm the pressures were greatly elevated in both upper extremities, with normal readings in the internal saphenous vein in the 2 cases in which measurements were made at this point, indicating compression of the superior vena cava. Similar findings were recorded in two cases of mediastinal neoplasm, one a lymphoma and the other a metastatic carcinoma. Villaret and Martiny³ review several cases in which the effect of aneurysm in altering peripheral venous pressures again is demonstrated. They also mention a case of tuberculous mediastinitis in which strangulation of the superior vena cava caused a pressure of 300 mm. of water in the veins of the arm as compared to a pressure of 200 mm. in the internal

*From the Georgetown University Hospital and the Gallinger Municipal Hospital. Received for publication July 20, 1933.

Read before the American Heart Association, at San Francisco, June 10, 1933.

saphenous vein. Villaret and Desoille⁴ mention difference in venous pressures in the arms as a common finding in cases of mediastinal tumors and cite a case of aortic aneurysm in which the venous pressures in the right and left arms, respectively, were 70 and 150 mm. of water. Ferris and Wilkins⁵ report, among other interesting cases, three in which mediastinal tumors caused significant differences in the venous pressures of the arm as compared to those of the leg. One was a case in which the thyroid was substernal, with pressures of 105 and 50 mm. of water, respectively, in the antecubital and femoral veins. The second was a case of mediastinal chorionepithelioma invading the superior vena cava, with measurements of 230 mm. (antecubital) and 45 mm. (femoral).

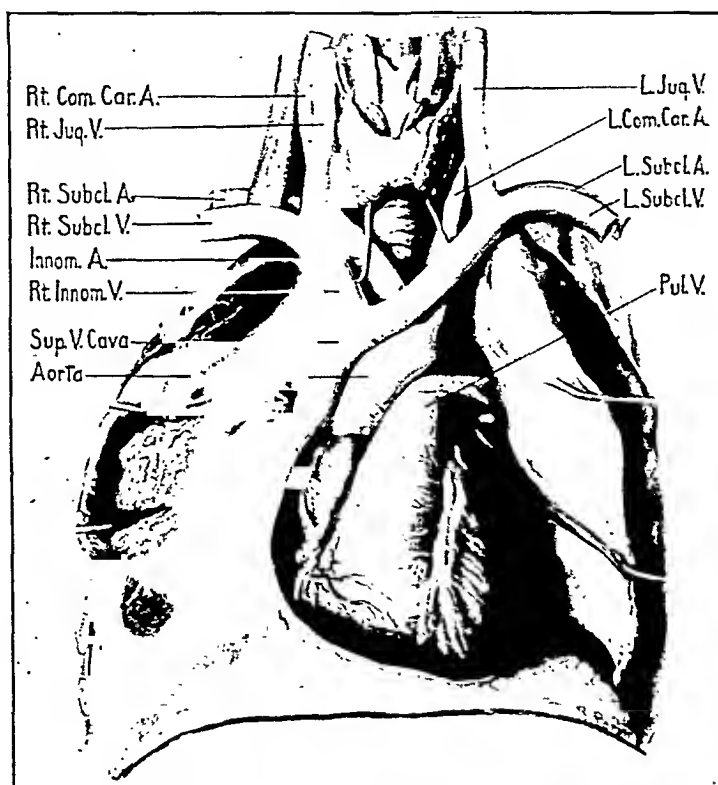


Fig. 1.—Anterior view of mediastinal structures.

The third was a case of bronchogenic carcinoma invading the superior vena cava, with measurements of 350 mm. (antecubital) and 80 mm. (femoral). Apparently, comparisons of the venous pressures in the two arms were not made in these cases. Burwell⁶ reports a case of lymphoma of the superior mediastinum in which the venous pressures in mm. of water were as follows: Right antecubital, 360; left antecubital, 215; left femoral, 60.

In this present study, in which comparisons similar to those of the authors quoted above are included, venous pressure measurements were made by the method of Griffith, Chamberlain, and Kitchell.⁷ A carpenter's level and a ruler were employed in order to ensure use of the same

plane on the two sides of the thorax and in the thigh for comparison of measurements. Readings were taken consecutively in the antecubital fossae and one of the femoral veins, the same instrument being used for each measurement on a given patient. The whole procedure required ten or fifteen minutes. This length of time is not sufficient to account for significant differences in pressures in the veins of the various extremities caused by alterations in the factors which normally control venous blood pressure, so that readings may be interpreted as if they had been taken simultaneously. Using this method in twelve patients without physical signs or roentgenographic evidence of disease which might cause alteration of the venous pressure in any of the extremities, I have found that the venous pressures in the two arms did not differ by more than 10 mm. of water in any case and that the pressure in the femoral vein tended to be a little higher than the pressure in the antecubital veins. In one case it was as much as 40 mm. of water higher, without apparent cause. These findings agree on the whole with those of Griffith, Chamberlain, and Kitchell⁸ and of Burwell.⁶ The series of fifty-two cases of mediastinal lesions in which clinical manifestations indicated the presence of a possible cause for differences in the venous pressures in the antecubital and femoral veins is included in Table I.

TABLE I

CASES IN WHICH THERE WAS A POSSIBLE CAUSE FOR DIFFERENCES IN VENOUS PRESSURE IN EXTREMITIES

	CASES
Aneurysm	27
Aortic dilatation	
Syphilitic aortitis	4
Hypertension	5
Mediastinal tumor (lymphoma)	7
Mediastinal tumor (carcinoma)	1
Undetermined	2
Superior sulcus tumor	1
Cold abscess	1
Substernal goiter	1
Carcinoma of esophagus	1
Patent ductus arteriosus	1
Pericarditis	1
	—
	52

VENOUS PRESSURES IN CASES OF ANEURYSM

Venous pressure measurements were made in both upper extremities in 27 consecutive cases of aneurysm of the thoracic aorta or innominate artery, and in 18 of these cases measurement also was recorded in one of the femoral veins. Careful roentgenographic and fluoroscopic examinations were made in all cases as a part of the clinical study leading to diagnosis. The results of the venous pressure measurements are shown in Table II. In Cases 1 to 10, inclusive, the aneurysm involved the

ascending aorta; in Cases 11 to 17, inclusive, the aortic arch; in Cases 18 to 24, inclusive, both the ascending aorta and the arch; in Case 25, the descending thoracic aorta; and in Cases 26 and 27, the innominate artery.

In 23 cases (85 per cent) the venous pressure measurements in the upper extremities showed significant differences, ranging from 25 to 220 mm. of water. It is important to note that a significant difference in arterial blood pressures in the two arms is a much less common finding. A difference of 10 mm. of Hg, or more, in either systolic or diastolic pressure was found in only 7 of the 27 cases (26 per cent). This group includes the 9 cases in which measurements were not made in the femoral vein. In 5 of the 23 cases (21.7 per cent) the venous pressures were

TABLE II
VENOUS PRESSURES IN TWENTY-SEVEN CASES OF ANEURYSM

CASE NO.	VENOUS PRESSURES (MM. OF WATER)			CASE NO.	VENOUS PRESSURES (MM. OF WATER)		
	RT. ARM	LEFT ARM	FEMORAL		RT. ARM	LEFT ARM	FEMORAL
1	95	100	55	15	138	95	45
2	160	150	50	16	30	55	
3	250	210	45	17	170	200	
4	55	155	110	18	210	115	70
5	90	115		19	78	125	
6	238	275	45	20	165	160	85
7	15	85		21	205	210	60
8	80	50	45	22	120	205	50
9	300	120	60	23	220	150	
10	320	100	90	24	205	265	275
11	70	135	125	25	55	120	
12	60	270		26	150	65	60
13	85	160	100	27	90	25	45
14	84	122					

higher than normal in both arms, indicating severe compression of the superior vena cava or both innominate veins. In 10 cases (43.5 per cent) the venous pressure was higher than normal in one arm and normal in the other, indicating severe compression of one innominate vein without demonstrable compression of the superior vena cava and other innominate vein. In the remaining 8 cases (34.8 per cent) in which there were significant differences in pressures in the two arms, the pressures were all within normal limits, indicating probably slight compression of one innominate vein only. The venous pressure was higher on the left side in 14 cases (61 per cent), and higher on the right side in 9 cases (39 per cent). The preponderance of higher pressures on the left side probably depends on the anatomic fact already mentioned, namely, the closer relationship of the left innominate vein to the aorta. As would be expected, in both of the cases of aneurysm of the innominate artery the venous pressure measurements indicated compression of the right innominate vein only.

Of the 18 cases in which the pressure in the femoral vein was measured, the femoral venous pressure was significantly lower than the pressure in either arm in 10 cases (55.6 per cent), and in 8 cases (44.4 per cent) it was not. Included in the first group were the 4 cases in which a significant difference in the venous pressures in the two arms was not discovered. In only one case (Case 24) was the femoral venous pressure higher than normal. This patient had severe congestive heart failure which persisted until he died and precluded the possibility of a low femoral venous pressure. However, the arm pressures showed a significant difference of 60 mm. of water in spite of the congestive heart failure.

The conclusion to be drawn from these findings is inescapable. Aneurysm of the aorta or innominate artery practically always causes changes in the venous pressures in the extremities by compressing the



Fig. 2.—Case 22. Aneurysm of ascending aorta and arch.

superior vena cava or one or both of its main tributaries. The only important exception would arise in cases in which the aneurysm compresses only the superior vena cava and in which congestive heart failure is simultaneously present. In such cases the venous pressure would be high in the tributaries of the inferior vena cava because of the congestive heart failure, and there would be no significant difference in pressures in the tributaries of the superior vena cava on the two sides of the body. In general, the larger the aneurysm, the greater the differences in venous pressures in the extremities.

The diagnostic value of comparison of venous pressures in the extremities naturally will depend upon how often the procedure is used. Certainly it is simple and inexpensive enough to encourage its frequent use. Probably it should be used in all cases of aortic regurgitation in which roentgenographic examination is not contemplated. The following brief summary of a case of aneurysm demonstrates its value.

ILLUSTRATIVE CASE

CASE 22.—W. G., a negro, aged 60 years, was admitted to Gallinger Municipal Hospital March 17, 1937. He had been working as a furniture mover until one week before admission, when he had suffered a sudden attack of unconsciousness which came on while he was working. On recovering consciousness, after about 10 minutes, he had noticed that his right arm and leg were paralyzed. The remainder of the history was irrelevant except that he had had a chancre and inadequate antisyphilitic treatment many years in the past. Physical examination revealed the usual evidences of partial right hemiplegia. The arterial blood pressure was 200/100; there was hypertensive retinopathy, grade 2; the heart was slightly enlarged; and a murmur typical of aortic regurgitation was audible. There was slight edema of the left hand, believed at first to be the result of the hemiplegia.* However, the venous pressures in mm. of water were found to be 205 in the left arm, 120 in the right arm, and 50 in the femoral. These findings suggested the possibility of aneurysm or, as seemed less likely, some other mediastinal lesion causing compression of the superior vena cava and left innominate vein. Subsequent fluoroscopic and roentgenographic examination substantiated the diagnosis of aneurysm (Fig. 2).

VENOUS PRESSURES IN CASES OF AORTIC DILATATION

In 9 cases studied, aortic dilatation insufficient to constitute aneurysm was diagnosed on roentgenographic examination. The results of venous pressure measurements in these cases are shown in Table III. Syphilitic

TABLE III

VENOUS PRESSURES IN NINE CASES OF AORTIC DILATATION

CASE NO.	VENOUS PRESSURES (MM. OF WATER)		
	RIGHT ARM	LEFT ARM	FEMORAL
28	65	95	
29	130	130	90
30	160	125	60
31	80	105	
32	210	250	260
33	88	90	
34	170	175	170
35	50	55	
36	115	115	

aortitis was present in 4 cases, and severe hypertension in the other 5 cases. These causative factors accounted for 2 and 3 cases, respectively, in which significant differences were found in the venous pressure measurements. In the remaining 4 cases significant differences were lacking. Congestive heart failure was present in Cases 32 and 34 to account for elevation of femoral venous pressure. In the latter case repeated measurements of the venous pressures in the arms failed to reveal a significant difference, and the pressures dropped within normal limits as the heart failure improved. Apparently aortic dilatation alters peripheral venous blood pressure less commonly than aortic aneurysm.

*Unilateral edema on the paralyzed side is common, particularly in the upper extremity, in cases of hemiplegia. However, Weiss and Ellis⁹ have shown that when such edema is the result of the hemiplegia the arterial and venous blood pressures are not significantly different in the upper extremities.

However, it must be kept in mind as a possible cause in cases in which comparisons of venous pressure measurements in the extremities are made for diagnostic purposes.

VENOUS PRESSURES IN CASES OF OTHER MEDIASTINAL LESIONS

In 16 cases of miscellaneous mediastinal lesions other than aneurysm or aortic dilatation, measurements of venous pressures in the two arms were compared, and in 13 of these cases measurement of femoral venous pressure also was obtained. The results of these measurements are shown in Table IV.

In 7 cases the diagnosis was mediastinal lymphoma, including 3 cases of Hodgkin's disease, 2 cases of acute lymphatic leucemia, 1 case of lymphosarcoma, and 1 case of malignant lymphoma of undetermined type. In this last case roentgenokymographic examination was necessary to exclude the diagnosis of aneurysm. In all 7 cases of lymphoma

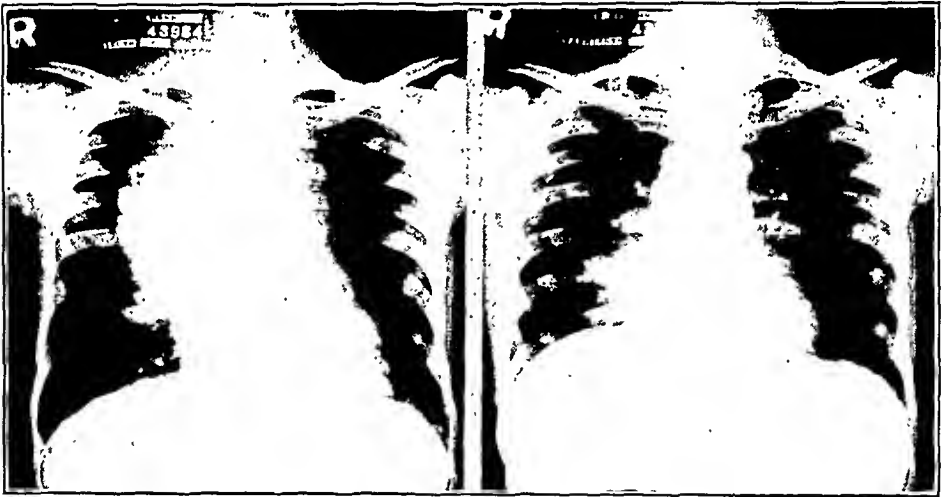


Fig. 3.

Fig. 4.

Fig. 3.—Case 38. Hodgkin's disease before roentgenotherapy.

Fig. 4.—Case 38. Hodgkin's disease after roentgenotherapy.

the effects of compression of the superior vena cava or one of its main tributaries on the venous pressures in the extremities were evident. In 5 cases the venous pressure was considerably elevated and nearly identical in both arms and was within normal limits in the femoral vein, probably indicating compression of the superior vena cava. In the other 2 cases the venous pressure was higher than normal in one arm and within normal limits in the other arm and femoral vein, indicating compression of one innominate vein.

Several of the cases of lymphoma demonstrated a further use, mentioned in a previous report,¹⁰ of comparison of repeated measurements of venous pressures for the purpose of showing the degree of response of mediastinal tumors to roentgenotherapy. For example, in one case of Hodgkin's disease (Case 38) with roentgenographic evidence of marked

enlargement of the mediastinum (Fig. 3), the venous pressures were 210 mm. in the arms and 100 mm. in the thigh. Several months later, after roentgenotherapy, the venous pressure measurements were as follows: right arm, 117 mm.; left arm, 93 mm.; femoral, 183 mm. This indirect evidence of shrinkage of the mediastinal tumor was verified by roentgenographic examination (Fig. 4). The rise in pressure in the femoral vein probably was the result of compression of the inferior vena cava by enlarged intra-abdominal lymph nodes.

In Case 44 the diagnosis during life was mediastinal lymphoma, probably Hodgkin's disease. The venous pressure measurements were indicative of compression of the superior vena cava, but no anatomic reason could be found for the high pressure (195 mm. of water) in the femoral vein. However, at post-mortem examination the patient was found to have carcinoma of the kidney (hypernephroma) with massive

TABLE IV
VENOUS PRESSURES IN SIXTEEN CASES OF OTHER MEDIASTINAL LESIONS

CASE NO.	DIAGNOSIS	VENOUS PRESSURES (MM. OF WATER)		
		RIGHT ARM	LEFT ARM	FEMORAL
37	Mediastinal lymphoma	55	195	60
38	Mediastinal lymphoma	210	210	100
39	Mediastinal lymphoma	175	80	45
40	Mediastinal lymphoma	160	160	80
41	Mediastinal lymphoma	190	190	45
42	Mediastinal lymphoma	235	235	50
43	Mediastinal lymphoma	180	180	55
44	Metastatic carcinoma	375	370	195
45	Undetermined	430	430	70
46	Undetermined	460	450	140
47	Rt. sup. sulcus tumor	180	50	60
48	Cold abscess	90	90	120
49	Substernal goiter	135	130	140
50	Cancer of esophagus	102	92	
51	Patent ductus arteriosus	90	120	
52	Pericarditis	320	130	

involvement of the mediastinal lymph nodes, accounting for the roentgenographic appearance of lymphoma, and with direct invasion and partial occlusion of the inferior vena cava, explaining the elevated pressure in the femoral vein.

Cases 45 and 46 were similar, as far as venous pressure measurements are concerned, to most of the preceding cases of mediastinal tumor; there was evidence of marked compression of the superior vena cava in the elevated, nearly identical venous pressures in the upper extremities, and normal pressure in the femoral vein. However, roentgenographic and fluoroscopic examinations yielded inconclusive results. In Case 45 the roentgenogram (Fig. 5) showed a shadow in the right superior mediastinum suggestive of a dilated superior vena cava, but the cause for this was not discovered. In Case 46 the clinical picture was that of sudden obstruction of the superior vena cava, with venous en-

gorgement and edema of the head, neck, and upper extremities. Roentgenographic and fluoroscopic findings were suggestive of an inflammatory lesion of the superior mediastinum, and this diagnosis was sup-



Fig. 5.—Case 45. Roentgenogram showing dilated superior vena cava.



Fig. 6.

Fig. 7.

Fig. 6.—Case 47. Right superior sulcus tumor.

Fig. 7.—Case 47. Roentgenogram showing destruction of right half of upper three dorsal vertebrae and first three ribs.

ported by the rapidity with which the patient grew worse and by the fact that death soon occurred. However, complete proof was lacking, and a post-mortem examination was not performed.

In Case 47, the patient, a 45-year-old negro, had symptoms and signs of disease of the upper thoracic portion of the spinal cord on the right side. He also had the ocular signs of involvement of the cervical sympathetic nerves on the right side. Roentgenograms disclosed an opacity overlying the apex of the right lung (Fig. 6) and destruction of the right half of the upper three dorsal vertebrae and posterior portions of the first three ribs (Fig. 7). The high venous pressure in the right arm probably indicated compression or invasion of the right subclavian vein. Biopsy of a cervical lymph node showed a highly undifferentiated malignant neoplasm. This finding, together with the roentgenographic report and failure to discover evidence of a primary neoplasm in the gastrointestinal tract, kidneys, or elsewhere, led to a diagnosis of superior sulcus tumor.

Little comment is necessary in Case 48, one of tuberculous abscess of the posterior mediastinum. The normal venous pressure measurements are not surprising in view of the distance of such an abscess from the great veins of the thorax.

In Case 49 comparison of venous pressure measurements in the upper and lower extremities had unusual diagnostic value. The patient, a white woman, aged 57 years, had the clinical manifestations of severe hyperthyroidism complicated by moderately severe essential hypertension. In the course of routine studies of the circulation the pressure in the antecubital veins was found to be above normal (150 mm. of water), and the arm-to-lung and arm-to-throat circulation times were prolonged (19 seconds and 36 seconds, respectively). These findings were believed at first to indicate the existence of congestive heart failure, but when roentgenographic study of the thorax showed a substernal goiter, the possibility had to be considered that elevation of venous pressure and prolongation of circulation times were due to compression of the thoracic veins. However, subsequent measurements of venous pressures in the femoral and antecubital veins all were high, confirming the original impression of congestive heart failure. In this case the femoral venous pressure was needed for accurate diagnosis.

In Case 50 the venous pressure measurements in the upper extremities were not significantly different. The patient, an Italian, aged 64 years, was obviously hoarse, but his other complaints could not be well understood partly because of the extreme hoarseness and partly because of his difficulty with the English language. The venous pressures were believed to rule out the possibility of aortic aneurysm in this case. The correct diagnosis of carcinoma of the esophagus was made after observing the patient for a few days and by means of appropriate fluoroscopic examination.

In Case 51, the patient, a young man, was known to have a patent ductus arteriosus. Venous pressure measurements were made in both arms as a matter of academic interest when it was discovered that no

57594

arterial pulsations could be detected in the left upper extremity. Interestingly enough, the venous pressure was 30 mm. of water higher on this side than on the right. I have no explanation for these findings.

In Case 52 the patient, a white girl, had been ill for about a week with pneumoecol lobar pneumonia, when edema appeared in the right side of the face and right infraclavicular region. On the next day fluoroscopic examination of the thorax and pericardial paracentesis led to a diagnosis of suppurative pericarditis. Venous pressure measurements at this time in the right and left arms were 350 and 180 mm. of water, respectively. The following day a roentgenogram showed considerable compression of the right lung by the dilated pericardial sac (Fig. 8). On this day pericardiotomy was followed by a drop in the venous pressures to 320 mm. in the right arm and 130 mm. in the left.



Fig. 8.—Case 52. Massive pericardial effusion.

It seems likely that in this case the pericardial effusion, in addition to causing some compression of the superior vena cava or right atrium, distorted or compressed the right innominate vein. Post-mortem examination, almost two weeks later, disclosed no likelier explanation.

SUMMARY AND CONCLUSIONS

1. A review of the literature dealing with comparisons of venous pressures in the arms and legs in cases of mediastinal lesions is presented, and 52 original cases are reported.

2. In 27 consecutive cases of aneurysm of the aorta or innominate artery, there was a significant difference in the venous pressures in the two arms in 23 cases (85 per cent). In the remaining 4 cases, although the venous pressures were equal in the two arms, they were significantly higher than the pressure in the femoral vein. This finding of high

venous pressure in one or both arms and normal pressure in the femoral vein was present in more than half the cases (55.6 per cent) in which femoral venous pressure was measured.

3. Such alterations in venous pressure measurements are the result of compression of the superior vena cava or its tributaries without compression of the inferior vena cava. In general, the degree and type of alteration depend upon the size and location of the aneurysm.

4. Aortic dilatation insufficient to constitute aneurysm was observed in 9 cases, in 5 of which similar significant alterations in venous pressures were found.

5. The effects on venous pressures in 16 cases of other mediastinal lesions are presented. Such lesions, particularly tumors, are shown to alter venous pressure measurements in much the same way as aneurysm.

6. Repeated measurements of venous pressures are valuable in observing the response of some types of mediastinal tumor to roentgenotherapy.

7. Measurement of the venous pressures in the antecubital and femoral veins is a valuable aid in the diagnosis of mediastinal lesions.

REFERENCES

1. Middleton, W. S.: A Case of Aneurysm of the Aorta with Unusual Pressure Signs, *Wis. M. J.* 31: 37, 1922.
2. Villaret, M., Saint Girons, F., and Bosviel, G.: Peripheral Venous Pressure in Syndromes of Localized Venous Hypertension, *Bulletin Medical* 39: 821, 1925.
3. Villaret, M., and Martiny, M.: Peripheral Venous Pressure in Mediastinal Syndromes, *Presse méd.* 37: 249, 1929.
4. Villaret, M., and Desoille, H.: Venous Pressure Measurement, *Presse méd.* 40: 1477, 1932.
5. Ferris, E. B., Jr., and Wilkins, R. W.: The Clinical Value of Comparative Measurements of the Pressure in the Femoral and Cubital Veins, *AM. HEART J.* 13: 431, 1937.
6. Burwell, C. S.: A Comparison of the Pressures in Arm Veins and Femoral Veins with Special Reference to Changes During Pregnancy, *Ann. Int. Med.* 11: 1305, 1938.
7. Griffith, G. C., Chamberlain, C. T., and Kitchell, J. R.: Simplified Apparatus for Direct Venous Pressure Determination Modified From Moritz and v. Tabora, *Am. J. M. Sc.* 187: 371, 1934.
8. Griffith, G. C., Chamberlain, C. T., and Kitchell, J. R.: Observation on the Practical Significance of Venous Pressure in Health and Disease with a Review of the Literature, *Am. J. M. Sc.* 187: 642, 1934.
9. Weiss, S., and Ellis, L. B.: The Circulatory Mechanism and Unilateral Edema in Cerebral Hemiplegia, *J. Clin. Investigation* 9: 17, 1930.
10. Hussey, H. H.: Clinical Application of Venous Pressure Measurement, *M. Ann. District of Columbia* 5: 232, 1936.

BILATERAL CAROTID SINUS DENERVATION IN A PATIENT HAVING SYNCOPAL ATTACKS AND A CONGENITAL VASCULAR ANOMALY

REPORT OF AN UNUSUAL CASE*

ALBERT H. ELLIOT, M.D., NEVILLE T. USSHER, M.D.,
AND CALEB S. STONE, M.D.
SANTA BARBARA, CALIF.

THE following history of a patient suffering from syncopal attacks is presented because of the interesting combination of hyperirritability of the carotid sinus mechanism together with a congenital vascular abnormality affecting the head and upper extremities. The effects upon this syndrome of bilateral denervation of the carotid sinuses will be described.

REPORT OF CASE

I. S., a male Mexican laborer, 26 years of age, was admitted to the Santa Barbara General Hospital in July, 1935, with the complaints of fainting spells, visual disturbances, and transitory weakness of the arms and legs.

The family and past histories were irrelevant.

While picking lemons five months previously there was sudden loss of vision which lasted but a short time. This was followed by episodes of trembling of the hands, weakness of the legs, and foggy or double vision. These symptoms lasted only a few minutes, but occurred several times weekly and proved so incapacitating as ultimately to make work impossible.

On several occasions the visual disturbance was followed by momentary loss of consciousness which occurred most commonly when he was standing, occasionally after a heavy meal when sitting, but never when lying down. He did not believe that these attacks were accompanied by convulsions, frothing at the mouth, or relaxation of the sphincters. Occasionally they were preceded by dyspnea. He had found that assuming a supine position prevented fainting and relieved the visual disturbance.

On physical examination neither blood pressure readings nor a radial pulse were obtainable in either arm. The blood and urine were normal. The spinal fluid was clear, not under increased pressure, and acellular. The colloidal gold curve was flat. Kahn precipitations, performed on blood and spinal fluid, were negative.

Six weeks later he was readmitted to the hospital because episodes of amblyopia, vertigo, and fainting, either singly or together, had recurred repeatedly.

The absence of pulsation in the major vessels of the upper extremities was again noted, and it was discovered that pressure over either or both carotid sinuses resulted in convulsive movements and syncope.

*From the Santa Barbara General Hospital and the Research Department of the Santa Barbara Clinic.

Received for publication July 20, 1938.

Read before the American Heart Association, at San Francisco, June 10, 1938.

The basal metabolic rate was minus 26 per cent. Venous blood sugar levels before and at hourly intervals following the ingestion of 100 gm. of glucose were 100, 117, 80, and 95 mg. per cent, respectively. Roentgenologic studies of the skull and chest disclosed a bony bridging of the sella turcica. There was no evidence of cervical ribs. The left ventricle was slightly enlarged, but the aortic arch was normal in pulsation and shape as viewed in the anteroposterior and oblique positions.

The patient was then referred to the vascular clinic of the Cottage Hospital where the following observations were made: There was pronounced pallor of the ocular fundi. A slight expansile pulsation, accompanied by a faint thrill, could be felt in the right carotid triangle. There was audible here a loud bruit with systolic accentuation which disappeared when pressure was applied just above the clavicle. The jugular veins were not visible. No pulsation could be felt over the left carotid artery, the temporal arteries, or the subclavian artery and its branches on either side. The blood pressure could not be obtained. Oscillometric readings on the arms were extremely low, the needle moving but half a division at the wrists. Vigorous pulsations were felt in the major arterial trunks of the legs and feet. The blood pressure in the legs averaged 220/120 when measured with the patient in the supine position.

To determine whether vascular spasm was an element in the production of this peculiar clinical picture, the patient, partially unclothed, was exposed to an environmental temperature of 18.2° C. for one hour, after which heat was applied to the trunk by means of a heated cradle. The temperature of the fingers of the right hand rose from 17.0° C. to 31.4°, and that of the fingers of the left hand rose from an initial level of 29° to 30.8° C. No increase in the oscillometric readings occurred after vasodilatation was induced, nor was it possible to obtain a pulse in the arms after giving nitroglycerin by mouth. It thus appeared certain that the lack of pulsation in the vessels of the upper extremities was not due to vascular spasm. The satisfactory rise in the skin temperature of the finger tips indicated that increase in blood flow to the hands, resulting from maximum vasodilatation, was of normal magnitude.

These observations suggested that the carotid and subclavian arteries took their origin from a common trunk arising from the aorta and that the orifice of this vessel was stenotic. Such an anomaly could explain the lack of pulsation in these vessels and the presence of the thrill and murmur above the clavicle.

Nature of the Syncopal Attacks.—Pressure over either carotid sinus resulted in seizures which the patient said were identical with his previous spontaneous attacks. The induced attacks were always similar in regard to the sequence of events and their time relationship with each other. Firm sustained pressure over either sinus area produced in four or five seconds slow, deep, regular breathing which persisted as long as pressure was maintained. Usually a few seconds later there was slight blanching of the face. The intensity, however, was difficult to evaluate because of the swarthy complexion. With continuance of pressure, tonic convulsive movements, appearing first in the legs, spread rapidly to the upper extremities, to be followed immediately by upward rotation of the eyeballs, dilation of the pupils, and, if the patient was sitting or standing, loss of consciousness. If pressure was still maintained, hyperpnea and convulsive movements persisted unabated. With release of pressure complete recovery was rapid, consciousness returning simultaneously with the subsidence of the other manifestations. The interval between the initiation of sinus pressure and the onset of syncope was usually about fifteen to twenty seconds. Light or intermittent pressure upon the sinus did not induce syncope nor convulsive movements, but some degree of hyperpnea always resulted. Likewise, syncope could not be induced if the patient was in the supine position.

TABLE I
CHANGES IN BLOOD PRESSURE AND PULSE RATE DURING INDUCED ATTACKS, SHOWING EFFECTS OF DRUGS AND OPERATIVE INTERVENTION

DATE	PROCEDURE	RESTING		PRESSURE RIGHT SINUS MAX-IMUM CHANGE		PRESSURE LEFT SINUS MAX-IMUM CHANGE		PRESSURE BOTH SINUSES MAX-IMUM CHANGE		COMMENT
		BL. P.	PULSE RATE	BL. P.	PULSE RATE	BL. P.	PULSE RATE	BL. P.	PULSE RATE	
10/21/35		190 120	112	120-150 0	40-50	120 0	80-85	115 0	40	Hyperpnea, paling, tonic convulsive movements, syncope. Pressure either side gives similar sequence.
10/23/35	Epinephrine, 0.6 mg. intramuscularly	260+ 140	104					135 0	60	Induced attacks not influenced by epinephrine.
10/29/35	Belladonna for 2 days. Atropine gr. 1/25 per os	205 120	84	185 100	100	170 100	84	175 95	64	Syncope could not be induced. Slight hyperpnea only with bilateral pressure.
10/31/35	Acetyl-β-methylcholine chloride 0.1 gm. intramuscularly	175 105	105					140 0	80	Hyperpnea and syncope easily induced.
11/26/35	Right denervation on 11/11/35	200 115	114	No change	No change	120 50	50			Pressure on right, no symptoms. Pressure on left, hyperpnea and syncope.
1/31/36	Left denervation on 1/8/36	180 90	105	No change	No change	No change	No change	200 105	84-80	Attacks can no longer be induced. Pulse slows slightly on bilateral pressure.

As previously stated, pressure over either sinus produced a similar train of events, but the concurrent changes in pulse and blood pressure differed slightly. With pressure upon the right sinus area, the systolic blood pressure as measured in the legs fell by as much as 40 to 80 mm. and the diastolic pressure usually became unobtainable. The pulse slowed to as few as 40 beats per minute. With release of pressure the rebound in blood pressure and pulse rate to the initial levels was immediate. Massage of the left sinus area was followed by a fall in pressure of similar magnitude, but the pulse slowing was less pronounced, averaging 20 beats per minute. With simultaneous pressure upon both sinuses there was some degree of summation of these effects. The magnitude of these changes is indicated in Table I. Electrocardiographic tracings taken during periods of maximum pulse slowing showed a simple depression of impulse formation in the sinus node. The rhythm remained regular and intraventricular conduction was unaffected.

The effect of various drugs upon induced attacks was studied. After the intramuscular injection of epinephrine, attacks could be induced with facility. The only change noted was that the pulse slowing was less pronounced. Atropin in large doses partially prevented the fall in blood pressure and pulse rate. Loss of consciousness could no longer be produced by bilateral pressure, and the hyperpnea was appreciably lessened. Acetyl- β -methylcholine chloride was used in large doses without appreciable influence upon the attacks. These observations are summarized in Table I.

Effect of Denervation of the Right Carotid Sinus.—On Nov. 11, 1935, denervation of the right carotid sinus was carried out under local anesthesia. The common carotid artery, just above the clavicle, was found to be slightly dilated and pulsating fairly vigorously. It then narrowed rather abruptly to approximately one-half the diameter of a normal artery, pulsation at this point and beyond being feeble. There was no communication between the artery and the jugular vein nor was the course of either vessel through the neck abnormal. Dissection of the carotid sheath and traction upon the artery in the region of the bifurcation caused hyperventilation and changes in the pulse and blood pressure which were exactly the same as those previously induced by pressure. Compression of the artery below the bifurcation was without effect. Electrocardiograms during these procedures were similar to those previously obtained. After the injection of novocaine about the sinus area periarterial stripping of the sheath was accomplished without further incident. Histologic examination of the removed tissue showed that it contained the carotid body and immediately related nerve fibers.

Course.—During the succeeding seven days in the hospital the blood pressure in the legs gradually rose from 185/95 to 225/135. On November 26, fifteen days after operation, the patient reported that he had been without symptoms except for one attack of vertigo and inability to flex the fingers of the left hand on the preceding day. At this visit the blood pressure, when the patient was supine, averaged 190/120. Firm pressure at the angle of the right jaw was entirely without result. During the succeeding month he had attempted to work, but his previous symptoms quickly returned with their former vigor. His pulse was found to be accelerated to 100 beats per minute, or more, on most occasions, as compared with the preoperative average of 80 to 90 beats per minute. The blood pressure in the legs remained at the same level. Pressure over the left carotid sinus area resulted in the usual attacks.

Denervation of the Left Carotid Sinus.—Because the patient's symptoms had not been appreciably improved by the first operation, the left carotid sinus was denervated on Jan. 8, 1936. Dissection of the neck disclosed a narrowed, pulseless, left common carotid artery. Its anatomic relationships with surrounding structures

were apparently normal. The dramatic course of events which occurred during the operation may best be expressed by the following protocol:

TIME	BLOOD PRESSURE	PULSE RATE	NOTES
9:10 A.M.	190/135		Excited; being prepared for operation.
9:30	260/140	129	Anesthesia of skin.
9:40	210/120	150	Dissecting sheath. Some hyperventilation.
9:50	160/110	135	Hyperventilation; sobbing and clenching of fists.
9:55	150/130	120	Artery being dissected out. Pulse suddenly slowed, then became imperceptible. Generalized tetanic convulsion. Pulse returned in about 30 seconds. Whiffs of carbogene.
10:02	190/150		Pulse slowing and weakening momentarily. Bifurcation dissected free.
10:03	190/150		Novocain into sinus.
10:13	260/150	150	Periarterial stripping begun.
10:35	260/160	132	Comfortable.
11:00	260/165	129	Dissection completed.

Course.—The patient has been observed over a fourteen-month period since the second operation. Blood pressure determinations were made at intervals of four hours during the first three postoperative days. The pressure remained at the preoperative level. During the succeeding month there were no syncopal attacks. For the following eight months the patient was able to work, but complained of transitory partial blindness and intervening periods when "things looked dark." At this time cataracts developed rapidly in both eyes, leading to total blindness. The cause of this unexpected complication remains unexplained.

Syncopal attacks, similar in all respects to those which occurred before operation have been experienced on approximately ten occasions. The last attack was followed by a left-sided hemiplegia from which recovery was complete in three weeks. At present pressure over either or both carotid bulbs is without effect upon respiration or blood pressure. The pulse slows slightly with bilateral pressure, but syncope can no longer be induced. The blood pressure in the legs as measured at frequent intervals during the fourteen-month period has shown a slight but definite downward trend. The last readings, taken with the patient in the supine position, averaged 160/100. The pulse rate has remained uninfluenced. It should be noted that this fall in pressure is not attributable to cardiac weakness.

DISCUSSION

It is not necessary to review the physiology of the carotid sinus mechanism except in so far as it bears upon derangement of the circulatory dynamics exhibited by this patient. Because of a vascular anomaly, the pressure within his sinuses was presumably low. If the sinus mechanism exerts a constant regulatory effect in the direction of preventing excessive intra-arterial pressures, the elevated blood pressure observed in the legs of this patient might be due to the lack of a pressure stimulus within the sinus sufficient to bring about a discharge of depressor impulses. Such a hypothesis at first sight seems reasonable in view of the fact that no rise in blood pressure occurred following denervation of

both sinuses. However, the studies of Leriche, et al.,¹ indicate that in man, as well as in the dog, the carotid sinus mechanism does not exert a constant regulatory effect upon the circulatory apparatus. They subjected five patients to bilateral carotid sinus denervation, and in three of these which were satisfactorily followed, changes in blood pressure and pulse rate were transitory only. Thus it would seem that the carotid sinus mechanism may be disrupted with impunity, so far, at least, as the danger of producing lasting hypertension or tachycardia is concerned. We may not, therefore, attribute the hypertension in our patient to inhibited sinus function. It is more likely that decreased flow through the vasomotor centers of the midbrain produced a state of generalized persistent vasoconstriction.

Two possibilities suggest themselves as explaining the occurrence of the syncopal attacks suffered by this patient. Cerebral ischemia, sufficient to induce unconsciousness, could conceivably result from sudden lessening of the carotid blood flow. This might occur when, in the upright position, the degree of physical activity did not insure the maintenance of a sufficiently high systolic pressure to drive the blood through the congenitally narrowed vascular system supplying the head. Such a mechanism would be similar to that in patients who faint from postural hypotension. The blood pressure in the legs of our patient rose 40 to 50 mm. when the upright position was assumed after lying supine, but, since pressures in the arm could not be obtained, we do not know whether a simultaneous diminution in blood flow occurred in the upper portion of the body, which, of course, is characteristic of postural hypotension.

The second possible mechanism is that at times a stimulus, the nature of which is unclear, acted upon the carotid sinuses and thus caused spontaneous attacks similar to those induced by pressure over the sinus areas. That such was the case seems probable. The patient stated that the subjective sensations accompanying the induced and spontaneous seizures were identical. Spontaneous attacks were preceded by difficulty in getting the breath, and on one occasion, after the patient had been standing for some minutes before a fluoroscopic screen, he began to breathe deeply and said that he felt dizzy and was about to faint. The hyperpnea continued for a minute or more, but consciousness was not lost. This was the only spontaneous attack seen by us. The appearance of the patient was similar to what it was during carotid sinus pressure. The complete disappearance of the spontaneous seizures for a month following the second operation and their infrequent occurrence since that time are likewise strong evidence that the carotid sinus was a factor. It is of course possible that both mechanisms were operative. This would explain the return of syncopal seizures, following operation, at a time when pressure upon the sinus areas was without effect upon the circulatory system.

Ferris, Capps, and Weiss² have classified carotid sinus syncope as being either of the cerebral type (syncope due to altered reaction of the brain cells dependent upon vasomotor changes in strictly localized areas or upon a response to efferent nervous impulses originating in the sinuses), or of the cardiac type (circulatory), in which unconsciousness is accompanied by, and presumably dependent upon, slowing of the heart and, usually, a fall in blood pressure. Fainting due to the latter mechanism is abolished by atropine. This was true in our patient, and the induced syncope was always accompanied by profound cardiovascular changes. He was therefore classified as an instance of the cardiac or circulatory type of syncope. Operative intervention was undertaken with the hope of interrupting this hypersensitive carotid reflex and of perhaps producing a lasting elevation of systolic pressure sufficient to drive blood through a congenitally narrowed vascular bed. The hope (although only partially realized) that by means of either or both of these effects a successful therapeutic outcome might be achieved justified surgical intervention of an experimental nature.

SUMMARY

Bilateral denervation of the carotid sinuses was performed upon a patient suffering from incapacitating syncopal seizures. The probable etiology of this condition was hyperirritability of the carotid sinus mechanism in association with a congenital obstruction to blood flow through the head and arms. The frequency and severity of attacks were greatly diminished over a period of fourteen months. Blood pressure and pulse rate levels were not appreciably altered. Bilateral cataracts developed after eight months, and a transient hemiplegia after ten months. Theoretic conceptions regarding the abnormal physiology in this case, and its attempted cure by surgical means, are discussed.

REFERENCES

1. Leriche, R., Froelich, F., and Fontaini, R.: *L'Enervation Simi; Carotidienne*, *Presse méd.* 43: 1217, 1935.
2. Ferris, E. B., Capps, R. B., and Weiss, S.: *Carotid Sinus Syncope and Its Bearing on the Unconscious State and Convulsions*, *Medicine* 14: 377, 1935.

THROMBOPHLEBITIS MIGRANS

CASE REPORT

LOUIS HIRSCHHORN, M.D., JAMES R. LISA, M.D., AND
RAYMOND J. GOLDSTEIN, M.D.
NEW YORK, N. Y.

THIS is a report of a case of thrombophlebitis migrans with unusual heart findings in which necropsy was performed. While these cases are not uncommon in the literature, post-mortem studies on them are rare.

CASE REPORT

Mrs. D. S., white, aged 54 years, was admitted to City Hospital on the service of Dr. W. L. Whittemore, in extreme heart failure, on May 25, 1937. Breathing was extremely difficult, cyanosis marked, the liver large and tender. Both legs were swollen and pitted on pressure. The right arm was swollen and warm. The blood pressure was not obtainable. The heart rate was 172 and the pulse rate 46, making a pulse deficit of 126. The following superficial veins were palpable as firm, pencil-like structures which could not be compressed: the right external jugular, right axillary, and all those of the right arm. The right axillary vein was tender to pressure. The legs were warm and had a red, blotchy appearance. Wherever veins were palpable, they were hard and incompressible. The diagnoses were (a) extreme heart failure and (b) multiple thrombophlebitis.

Eight cat units of digifolin were given intravenously. Within an hour the dyspnea was less pronounced, and the patient felt better. The heart rate was 140, the pulse rate 80, the pulse deficit 60. The pulse volume was good.

Additional History.—There had been moderate dyspnea and orthopnea for four years, becoming more severe during the preceding two weeks. The past history was otherwise negative except for diphtheria in childhood. The only treatment prior to the time of admission was "Christian Science."

Course.—Next day, May 26, the patient was given 8 cat units of digitan by mouth. The electrocardiogram (Fig. 1, *A*) was taken that evening. It showed ventricular tachycardia with a heart rate of 180. For the next three days the patient received 2 cat units of digitan and 0.2 gm. of quinidine daily, the latter to test for idiosyncrasy. The ventricular tachycardia and pulse deficit persisted (Fig. 1, *B*, *C*, and *D*; *D* was taken the morning of May 29). On May 29, 0.4 gm. of quinidine was given at 11:15 A.M., 1:15 P.M., 3:15 P.M., and 5:15 P.M., making a total of 1.6 gm. in six hours. Tracing *E* was taken in the evening; it showed numbers of nodal beats and a marked slowing of the heart. On May 30 the administration of quinidine in doses of 0.33 gm. three times a day was begun, with the result that normal sinus rhythm returned. Tracing *F*, taken May 31, and *G*, taken June 1, show this plainly.

With the appearance of sinus rhythm the pulse rate fell to 100, with no deficit, and the patient's condition was greatly improved. Quinidine in doses of 0.33 gm. three times a day maintained sinus rhythm. On two occasions when quinidine was discontinued ventricular tachycardia returned, and, with it, all the original symptoms. Each time quinidine in doses of 0.33 gm. three times daily restored sinus rhythm and brought about the same clinical improvement.

From Second Medical Service of Dr. W. Laurence Whittemore, and Pathological Laboratory, City Hospital, Department of Hospitals, Welfare Island, N. Y.
Received for publication July 25, 1938.

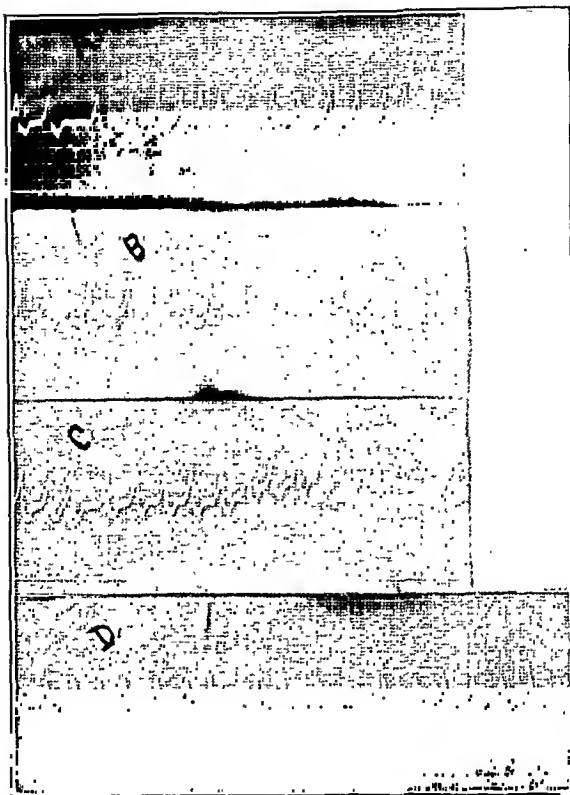


Fig. 1.—Lead I. *A*, May 26: after 8 cat units of digitalis, intravenously. Heart rate 180, radial pulse rate 40. *B*, May 27: digitalis, 8 cat units, total 16 cat units. Heart rate 180, pulse rate 80. *C*, May 28: digitalis, 2 cat units. *D*, May 29, morning: quinidine, 0.4 gm.

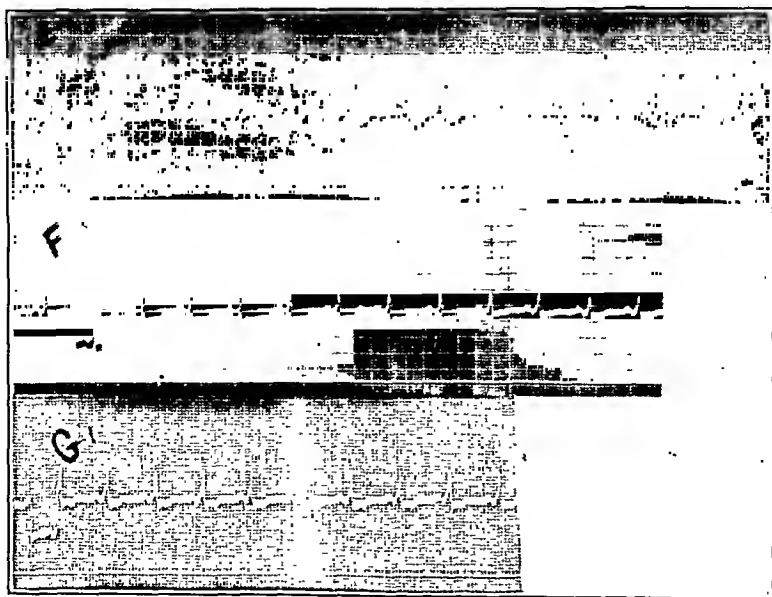


Fig. 1.—Lead I. *E*, May 29, evening: after 1.5 gm. of quinidine in divided doses. *F*, May 30: after additional quinidine (1 gm.). Heart rate 100, pulse rate 100. *G*, June 1: quinidine, 0.3 gm. three times a day. No pulse deficit.

During the remaining six weeks of her life the patient had a very difficult and eventful course. On four occasions she developed pain in the chest, fever, coughed up bloody, frothy sputum, and the lungs showed signs of consolidation.

The edema of the legs and right arm was at no time improved by diuretics, despite good diuresis. It subsided slowly and steadily, and the previously hardened veins softened.

On May 29 the left arm was painful, hot, and considerably swollen. These symptoms lasted for two weeks and then subsided slowly. On June 20, after a sharp temperature rise, two large abscesses of the back were drained.

The next episode was pneumonia with fluid in the chest. Dyspnea increased and the chest had to be tapped. The pleural fluid, at first serosanguineous, later became purulent and yielded indifferent streptococci on culture. Paracentesis was



Fig. 2.—Minute area of myocardial degeneration showing early necrosis of the fibers and infiltration by polynuclear cells. View from left ventricle.

performed every three days. Soon the face and eyelids became swollen. At this time the plasma albumin was 1.7 per cent, the globulin 2.8 per cent, and the blood pressure 115/70. The urine contained leucocytes, erythrocytes, casts, and albumin (graded 2 plus).

On July 6 the temperature continued to rise. The patient was irrational, incontinent, and icteric (icteric index 25). The pulse and respiratory rates increased, and on July 11 she died.

Laboratory Studies.—The blood Wassermann and Kahn reactions were negative. On May 26 chemical examination of the blood showed nothing abnormal. On June 28 the blood chlorides were 379 mg. per cent. On June 4 the bleeding time was three and one-half minutes and the clotting time four minutes. On June 1 the hemoglobin was 60 per cent, the erythrocyte count 3,650,000, and the leucocyte

count 13,900. The differential leucocyte count showed 96 per cent polymorphonuclear neutrophils (2 per cent of which were staff cells) and four per cent lymphocytes.

Autopsy (No. 4962).—There was moderate post-mortem rigidity. The finger nails were cyanotic. There was a greenish discharge from the nostrils. There were large decubital ulcers of the sacrum and right hip. The subcutaneous fat and muscles were normal. The peritoneum was dry and the abdominal organs were in normal position. The diaphragm was at the fourth right rib and fifth left interspace. Both external iliac veins contained ante-mortem gray-red adherent mural thrombi, extending down to the femoral rings and not completely occluding the lumina.

Heart: Weight, 375 gm. The sac contained 100 c.c. of clear fluid. The heart was moderately dilated, the epicardial fat normal in amount. The right chambers were normal, the valves not remarkable. The left auricle was enlarged, the endo-

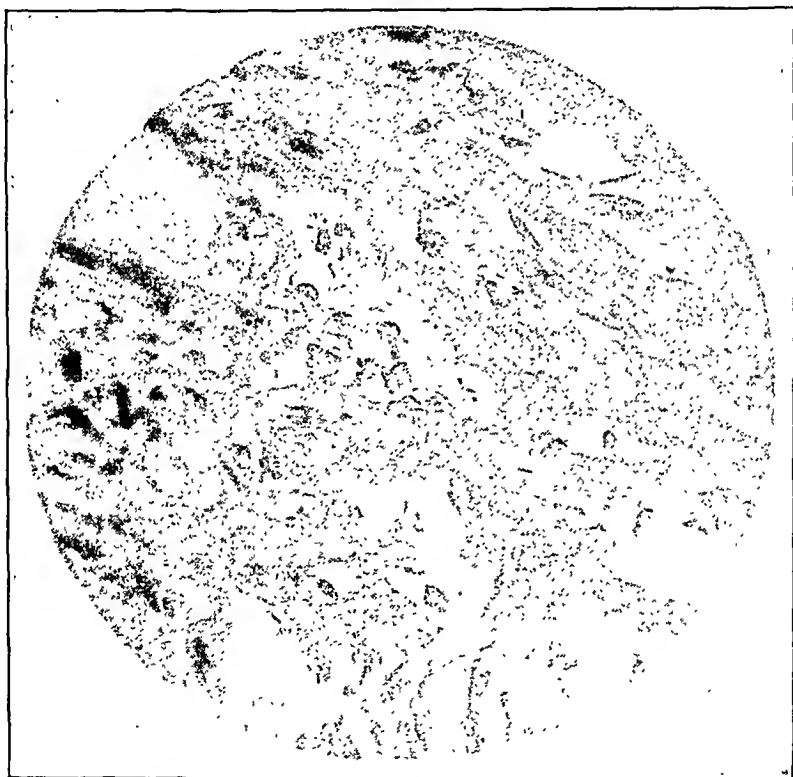


Fig. 3.—Lesion of similar nature in auriculoventricular node.

cardium thick, gray-white, and opaque. The mitral valve was stenotic, the cusps fused and leathery, the edges thick and rounded, the chordae tendineae short, thickened, and fused. Along the line of closure were several raised, soft, pinkish vegetations 2 to 3 mm. in size. The left and posterior aortic cusps were fused on the ventricular surface; the other cusps were normal. The myocardium was soft, flabby, pale yellow-red, of poor consistency and unscarred. The coronary mouths and arteries were normal.

Aorta: There was minimal atheroma, and the elasticity was well preserved.

Lungs: The right pleural cavity contained 200 c.c. of a cloudy fluid. The lobes were adherent by fine fibrous bands. The pleura was smooth and shiny. On section the color was pink. Scattered throughout all lobes there were small gray raised areas, and a moderate amount of exudate was present in the bronchi. The arteries and veins were free of thrombi. The weight was 800 gm.

The left pleural sac contained 1500 c.c. of greenish pus. The lung was collapsed against the vertebral column and covered by a thick green fibrinous exudate. On section the lower lobe was diffusely involved by a gray consolidation with small necrotic foci scattered throughout. No thrombi were demonstrable.

The bronchial lymph nodes were large, soft, and black.

Liver: Weight 1350 gm. It was moderately enlarged and soft. The gall bladder and ducts were normal.

Spleen: Weight, 100 gm. It was very soft. The cut surface presented a muddy gray appearance and the pulp scraped very easily.

Pancreas: Normal.

Adrenals: There was marked post-mortem disintegration.

Urinary System: The right kidney weighed 260 gm., the left 200 gm. In both kidneys there were several small cortical cysts and in the right there was a large subcapsular cyst measuring 5 cm. in diameter. The capsules stripped easily, leaving a smooth surface. The cortex appeared boiled, and the tissue markings were obscured. The pelvic mucosa was injected. The ureters and bladder were normal.

Internal generative organs: Except for a sessile polyp of the endometrium, the organs were not remarkable.

Gastrointestinal tract: Normal.

Histologic Examination.—Heart: The manifestations of rheumatic disease were in the final stage. There were numerous perivascular scars at the base of both ventricles and very few in the upper interventricular wall. In the left auricle there was a densely fibrosed subendocardial areolar zone. The mitral valve showed dense hyaline fibrosis, an occasional small calcified focus near the free edge, a few vascularized areas, and a vascular base wedge moderately infiltrated by small round cells. The left auricular muscle was greatly hypertrophied; the right ventricular, moderately.

The mitral valve showed a few fibrinous deposits on the auricular side.

Minute scars not associated with the vascular tree and apparently nonrheumatic in origin were found in the left ventricle. They were of all stages from well-vascularized connective tissue to dense hyaline scar.

Minute foci of acute myocardial changes were present in moderate numbers in both ventricles, the interventricular wall, and the auriculoventricular node. They involved small nests or individual fibers, which were replaced by a granular cytoplasmic mass invaded by polynuclear cells. In size and relationship to the vascular tree they resembled the small scars just described.

The arteries, veins, and endocardium presented nothing of note.

Lung: The lung was diffusely infiltrated by a fibrinopurulent exudate containing many gram-positive diplococci. There were very many areas of acute necrosis in the left lower lobe, without hemorrhage. Thrombi were not seen. Hemosiderin-bearing phagocytes were present in large numbers. Carbon pigment was dense in the perivascular and peribronchial regions, particularly at the hilum.

Liver: There were marked chronic passive engorgement and extensive fatty degeneration. The vessels were normal.

Kidney: Normal.

External Iliac Vein: Adherent to a portion of the wall was a young simple thrombus not undergoing organization. The wall, with the exception of destruction of the intima beneath the thrombus, was normal.

Anatomic Diagnosis.—Healed rheumatic myocarditis and valvulitis with mitral stenosis; acute myocardial focal degeneration; chronic passive congestion of lungs, liver, and spleen; acute bilateral pneumonia with empyema; anthracosis of lungs; acute cloudy swelling of liver and kidneys; decubital ulcers; multiple thrombophlebitis of superficial veins; bilateral thrombosis of external iliac veins.

REVIEW OF LITERATURE

Barker,¹ in a recent article, has given an excellent résumé of the literature on idiopathic thrombophlebitis which brings the subject up to the end of 1937. Up to and including 1935, twenty-two cases of this disease were recorded. For his study Barker selected seventy-nine out of 1,011 cases of thrombophlebitis. These seventy-nine were chosen because they occurred in patients in whom no demonstrable etiological factor such as infectious disease, a surgical operation, heart disease, varicose veins, or trauma was present. Half of the patients had a single attack, while the other half had recurrent attacks; one patient had had more than twenty episodes over a period of eighteen years. The veins involved included all the superficial veins of the body, arms, and legs. In 30 per cent of the recurrent cases there was pulmonary infarction, which was fatal in two cases. While no autopsy was obtained, Barker believed that the lung lesion was due to embolism from the veins of the extremities. Moorehead and Abrahamson,² in their series of four cases, reported lung involvement in two and thrombosis of the heart veins in one. Ryle³ found in five cases one instance each of thrombosis of the lung veins and heart veins. Collier⁴ and Ellison⁵ record one case of pulmonary vein thrombosis. Campbell and Morgan⁶ reported involvement of the cerebral and cardiac veins in a man 26 years of age. This patient's electrocardiogram showed rhythmic bigeminy. In Barber's⁷ case the cerebral veins were the first to be involved. Walker,⁸ Douglas-Wilson and Miller,⁹ and Powell¹⁰ reported a total of four cases, in all of which there was involvement of the superficial veins only. Harkavy's¹¹ patient had phlebitis of the veins of the left leg and thigh, and ascites. Six months later the left thigh was again involved. D'Abreu's¹² patient, a man of 52 years, had his initial thrombophlebitis in the left leg at 12 years of age. Then came later attacks at the ages of 43, 46, and 50. The terminal episode was gangrene of the right leg for which amputation was performed, following which the patient died. Autopsy revealed organized and canalized thrombi of the veins and arteries typical of thromboangiitis obliterans.

Idiopathic thrombophlebitis is a relatively benign condition, so that necropsy data on it are few. In the 101 cases cited above there was but one autopsy (D'Abreu's case). In eleven of Barker's cases, Barker removed a portion of thrombosed vein. Careful cultures of these remained uniformly sterile. Histologically, the lumen of the vein was occluded by an organized thrombus, and the wall of the vein was markedly infiltrated by connective tissue cells, as was the perivenous tissue. The process was indistinguishable from thromboangiitis obliterans except by the degree of reaction. These are the histologic changes of an end or late stage, which may account for the negative bacteriologic results. Barker stated his belief that the disease is strictly one of the peripheral veins and that visceral involvement is rare or nonexistent.

DISCUSSION

The patient of the present report was admitted to the hospital in extreme heart failure. She had thrombophlebitis of the following veins: right external jugular, right axillary, and all the superficial veins of the right arm and both legs. During her last seven weeks of life these cleared up slowly without residua. Four days after admission there developed a thrombophlebitis of all the superficial veins of the left arm which subsided after a course of two weeks.

The past history was one of moderate heart failure for four years, becoming severe during the two weeks before admission.

The course was interesting because of the four attacks of pulmonary infarction and the peculiar cardiac arrhythmia. These observations brought up the question whether or not we were dealing with visceral thrombophlebitis, especially of the pulmonary and cardiac veins. In the 102 cases of thrombophlebitis reported in the literature, pulmonary infarctions occurred in about 30 per cent. In the present case, definite clinical manifestations of infarction were present on four occasions, although none were demonstrated at necropsy. The presence of thrombosis of the iliac veins suggests that the emboli originated in the veins of the extremities. The absence of vascular disease in the lungs also supports the idea that the process was embolic rather than thrombophlebitic.

Thrombophlebitis of the coronary veins has been reported in a few instances.^{2, 3, 6} In each of these cases, however, the diagnosis was entirely clinical and was based on electrocardiographic evidence of peculiar arrhythmias. In the one autopsy case, that of D'Abreu,¹² the coronary veins were not affected. In the present instance also, the heart was entirely unaffected by thrombophlebitis.

In the absence, then, of coronary thrombophlebitis, some other explanation must be sought for the persistent ventricular tachycardia. That the rheumatic disease was the etiological factor seems unlikely, since histologically there were only healed lesions with no evidence of activity, and the clinical course did not resemble that usually seen in congestive failure in a heart anatomically deformed by an old, inactive rheumatic process. There were present, however, widely distributed minute foci of myocardial necrosis in the ventricles and similar foci in the auriculo-ventricular node. It is recognized that damage to muscle, whether cardiac, voluntary, or involuntary, results in hyperirritability. Foci of potential irritability were found in this heart and, in addition, similar foci in the node governing ventricular contraction. The minute scars of different ages found in the ventricles corresponding in size and shape to the acute lesions suggests also that the process was a continuous one. Its duration would correspond to that of the persistent ventricular tachycardia, namely, the seven weeks the patient was under observation. The etiology of the lesion remains obscure. There is no evidence either to prove or disprove the presence of infectious or toxic factors.

The correlation between the clinical results obtained during the administration of digitalis and quinidine and the histologic changes in the myocardium yielded interesting and valuable information. This patient had a rare arrhythmia, ventricular tachycardia. In this state she was in extreme heart failure with a heart rate of 180 and an almost imperceptible radial pulse rate of 40. Full doses of digitalis improved the circulation, subjectively and objectively, without altering the rhythm, i.e., the dyspnea diminished and there was a marked improvement in the radial pulse; its rate rose to 80, it became stronger, and the pulse deficit decreased. Quinidine effected a prompt and dramatic improvement in this patient's circulation. One gram a day restored sinus rhythm at a rate of 100 and abolished the pulse deficit. On two occasions, when quinidine was discontinued, the original rhythm and circulatory failure returned. Each time quinidine again restored sinus rhythm and compensation. We were dealing, then, with a permanent ventricular tachycardia, controlled by quinidine, which makes this case rarer. It seems at first glance paradoxical that quinidine, a heart muscle depressant, could be used to increase the efficiency of the heart. It seems justifiable, however, to conclude that the depressant action served to inhibit overactivity from hyperirritable foci. The case shows clearly that we ought to use this remedy more often in properly selected cases.

SUMMARY AND CONCLUSIONS

1. A case of thrombophlebitis migrans with necropsy is presented.
2. The thrombophlebitis was found to involve only the veins of the neck, arms, and legs.
3. Phlebitis of the viscera was absent.
4. Pulmonary episodes in such cases are undoubtedly due to emboli, and not to phlebitis of the pulmonary veins.
5. A rare arrhythmia, permanent ventricular tachycardia, was not due to thrombophlebitis of the cardiac veins, but to another, coexisting lesion.
6. From the therapeutic standpoint, the heart muscle stimulating action of digitalis and the effectiveness of quinidine in depressing hyperirritable heart muscle were demonstrated.
7. Thrombophlebitis migrans is a relatively benign disease, without definite etiology and without visceral lesions.

REFERENCES

1. Barker, N. W.: Primary Idiopathic Thrombophlebitis, *Arch. Int. Med.* 58: 147, 1936.
2. Moorehead, T. G., and Abrahamson, L.: Thrombophlebitis Migrans, *Brit. M. J.* 1: 586, 1928.
3. Ryle, J. A.: Thrombophlebitis Migrans, *Lancet* 2: 731, 1930.
4. Collier, W. T.: Thrombophlebitis Migrans Involving the Deep Veins of All Four Limbs, *Lancet* 2: 1408, 1931.

5. Ellison, J. B.: Thrombophlebitis Migrans Complicating Scarlet Fever, Brit. J. Dis. Child. 28: 207, 1931.
6. Campbell, M., and Morgan, D. G.: An Unusual Case of Multiple Thromboses, Guy's Hosp. Rep. 80: 34, 1930.
7. Barber, H.: A Case of Thrombophlebitis Migrans, Brit. M. J. 1: 281, 1932.
8. Walker, A. B.: Observations on Thrombophlebitis Migrans with Notes on a Case, Lancet 2: 936, 1932.
Two Cases of Thrombophlebitis Migrans, Glasgow M. J. 124: 66, 1935.
9. Douglas-Wilson, H., and Miller, S.: Thrombophlebitis Migrans, Practitioner 131: 204, 1933.
10. Powell, M. L.: Thrombophlebitis Migrans: An Illustrative Case, M. J. Australia 22: 336, 1935.
11. Harkavy, J.: Phlebitis and Thrombophlebitis Migrans, M. J. & Rec. 120: 64, 1924.
12. D'Abreu, A. L.: Relation of Thrombophlebitis Migrans to Thrombo-Angiitis Obliterans, Brit. M. J. 1: 101, 1934.
13. Low, G. C., and Cook, A. B.: Thrombophlebitis Migrans, Lancet 1: 584, 1931

VENTRICULAR EXTRASYSTOLES INDUCED BY ELECTRICAL STIMULATION OF THE EXPOSED HUMAN HEART ROTATED THIRTY DEGREES COUNTERCLOCKWISE ON ITS VERTICAL AXIS

CLAYTON J. LUNDY, M.D., IRVING TREIGER, M.D., AND
RICHARD DAVISON, M.D.

CHICAGO, ILL.

THE recording¹ of ventricular extrasystoles induced by electrical stimulation of known sites in the exposed human heart has had a marked influence on our understanding of electrocardiography. Because of this newer conception of the electrocardiographic configuration of ventricular extrasystoles, the classical conception of the electrocardiographic configuration of bundle branch block was reversed.² The important basic work of Barker, Macleod, and Alexander¹ has been partly confirmed.^{3, 4, 5} A report of experiments which confirm previous observations and add new information about this subject is herewith submitted.

REPORT OF CASE

The patient (D. M.), a white woman 39 years of age, had had advanced pulmonary tuberculosis involving the left lung since 1930. Pneumothorax was attempted on the left side in July, 1934, but was discontinued because of adhesions. A three-stage left-sided thoracoplasty was done in April and June, 1934.

Beginning in July, 1934, the patient complained of dyspnea upon exertion and of a pulling or pressure sensation around the heart. Cardiac physical examination after thoracoplasty was negative except for a systolic clicking sound heard at the apex of the heart and transmitted upward toward the base. This sound was heard only in the standing position and disappeared when the patient was lying down. It had not been heard previous to the thoracoplasty. The blood pressure was 110/76. The heart rate was 88 and the beat was regular. There were no other physical signs of cardiac embarrassment.

The cardiac diagnosis was pleuropericardial adhesions, and on July 29, 1937, an operation was performed by Dr. Richard Davison. At the time of operation the heart was freely exposed on its anterior and left lateral surfaces. The heart was found to be rotated counterclockwise on its longitudinal axis approximately 30°. This position gave free access to the left ventricle. There were some pleuropericardial adhesions which were severed. The pericardium was incised but no intra-pericardial adhesions were found. During the operation the condition of the patient remained excellent. The exposed heart functioned in a normal manner. Recovery was uneventful.

Four accurately observed points on the surfaces of the ventricles were stimulated with single make and break shocks (make voltage 2.3 volts, break voltage 8 volts). The resulting ventricular extrasystoles were re-

From the Municipal Tuberculosis Sanitarium of Chicago.
Received for publication July 26, 1938.

corded electrocardiographically in Leads I and III taken simultaneously with two electrocardiographs (Fig. 1). The four points of electrical stimulation were: Point one, located on the anterior wall of the base of the left ventricle; point two, on the anterior lateral wall of the left ventricle near the apex; point three, in the base of the posterior wall of the right ventricle 1.5 cm. to the right of the septum and posterior descending branch of the left coronary artery; and point four, on the anterior wall of the right ventricle about midway between Marvin and Oughterson's point A and Barker's point six.

Results of Stimulating Point One.—Point one was located on the anterior wall of the left ventricle near the base, about 1.5 cm. to the left of Barker's point one. Since the heart was rotated 30° in a counterclockwise direction on its vertical axis, this means that what would have been normally the posterior lateral basal region of the left ventricle was, under these circumstances, the anterior lateral basal region of the left ventricle. It may be observed that the configuration of the electrocardiogram from point one in this experiment has the same characteristics as that from Barker's¹ point one, which was taken with the heart in the normal position from the anterior lateral basal region of the left ventricle, whereas that from Lundy's point one (1L),⁴ also taken from a heart in the normal position, has the opposite configuration in spite of the fact that the point coincides rather closely with point one stimulated in this experiment in which the heart is rotated 30° in a counterclockwise direction. This latter observation, when compared with the results of stimulating point one under the conditions of this experiment, gives clinical confirmation of the work of recent observers⁵⁻⁹ who have shown that rotation of the heart within the thoracic cavity produces a change in the configuration of the electrocardiogram.

Results of Stimulating Point Two.—Point two was located on the anterior lateral wall of the left ventricle near the apex. Since the heart was rotated, this point corresponded to a point on the posterior lateral surface in a heart normally positioned. Point two was in the same region as Barker's point twelve, Marvin and Oughterson's³ point B, and Lundy and Baeon's⁴ point two. It is seen that with rotation of the heart 30° in a counterclockwise direction on the vertical axis, the electrocardiographic results are different. In our instance of point two the QRS complexes were divergent, with QRS in Lead I upright and QRS in Lead III inverted; while in the instance of point two of Marvin and Oughterson, they were convergent; QRS in Lead I was inverted and QRS in Lead III upright. The relationship of our results to those obtained by Barker from point twelve is mentioned under the discussion of our point two A.

It is important to observe that the results from stimulating points one and two support a previous experiment¹⁰ in which the QRS deflections

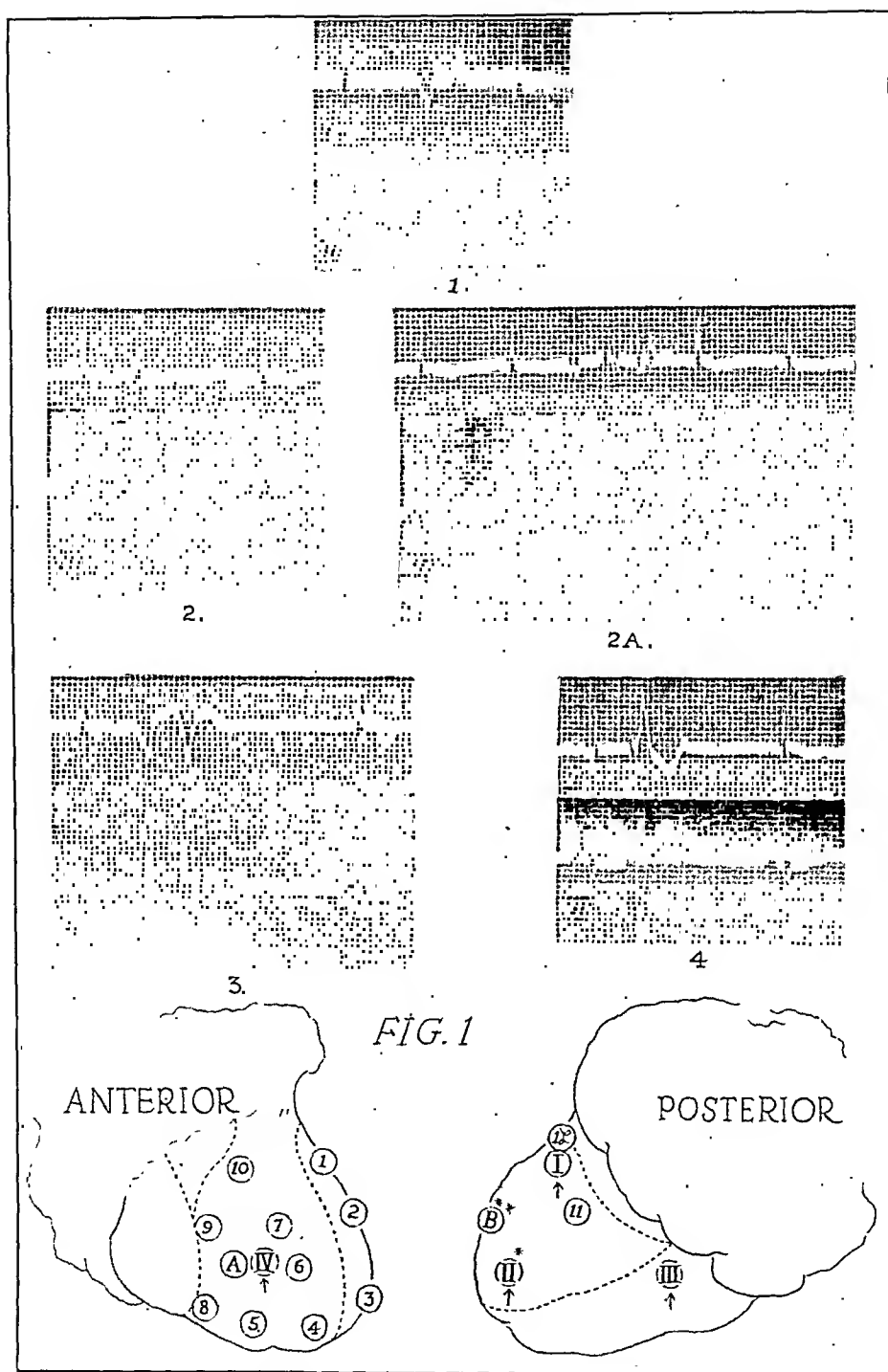


Fig. 1.—Points 1 to 12: Barker, Macleod, Alexander.

Points A and B: Marvin, Oughterson.

Points 1L and 2L: Lundy, Bacon.

Points I to IV: Arrows indicate points stimulated in these experiments.

*II and IIA same as Barker's point 12.

**2L same as point B.

were opposite in direction in Leads I and III when derived from the base of the ventricles, in contradistinction to those derived from the apex.

Point two A was located in the same site as point two. This extrasystole was produced with the heart rotated approximately 30° in a clockwise direction on its horizontal axis when viewed from the patient's left side, in addition to the 30° counterclockwise rotation on its vertical axis, i.e., when the apex of the abnormally positioned heart rose up into the operative wound. It is to be observed that in this doubly rotated position the extrasystolic QRS complex is inverted both in Leads I and III like that obtained by Barker from his point twelve, which is in a similar location to our point two. The important difference in the conditions of Barker's and our experiment was that in Barker's case the heart was not rotated, whereas in our case and under the circumstances of this second stimulation of point two, the heart was not only rotated 30° counterclockwise on the vertical axis but was also rotated 30° in a clockwise direction upon the horizontal axis. This observation seems to show that the latter rotation caused QRS to become inverted in Lead I when the extrasystole arose at point two. Another important fact revealed by these sets of circumstances is that rotation about the horizontal axis influenced the extrasystole in Lead I and the *usual* electrocardiogram in Lead III. A suitable explanation for this fact might be that the pathway followed by the summation of electrical events which take place when an extrasystole arises at the apex of the left ventricle is in approximately the opposite direction to that taken when the excitation wave travels over the normal pathway.

Of course it must be admitted that there was considerable difficulty in keeping the electrode on exactly the same point with the heart beating, and still more so when the apex rotated temporarily into the operative wound. There was not so much difficulty encountered when the base was stimulated. However, it must be asserted that within reasonable limits our points were accurately located, since in both instances the same results were observed twice.

Results of Stimulating Point Three.—Point three was located on the base of the posterior wall of the right ventricle 1.5 cm. to the right of the septum and posterior descending branch of the left coronary artery. So far as we know this is the first time that this area has been stimulated in the exposed human heart. One may question these results because the first extrasystole was not produced by electrical stimulation, since there is no mark to indicate that such was the base, and because the second extrasystole would have happened regardless of the presence or absence of electrical stimulation. It is also true that pairs of spontaneously occurring extrasystoles arose even without mechanical stimulation in other instances during these experiments. However, it will be noted that the elapsed time between stimulation and ventricular response varied con-

siderably in our experiment; this is true in all cases reported in the literature, and, since it is possible for immediate response to take place, it is our feeling that this is a true ventricular extrasystole produced by electrical stimulation of the posterior basal region of the right ventricle. Furthermore, we should like to point out the similarity of mechanically and electrically induced ventricular extrasystoles when initiated from approximately the same areas. Two examples occur, in that Fossier's points five and six are practically identical with Barker's¹ points eight and two.

Results of Stimulating Point Four.—Point four was located on the anterior wall of the right ventricle near the apex, about midway between Marvin and Oughterson's point A and Barker's point six. Our result further confirms their observations. It is of great interest that in spite of the rotation of the heart, stimulation of this region of the right ventricle gave a ventricular extrasystole with the same configuration as those elicited from the same region of the right ventricle when the heart was in normal position. In this connection it is also important to recall that in Barker's work the configuration of extrasystoles from six different sites in a large area on the anterior surface of the right ventricle had similar configurations. In the left ventricle the configuration of extrasystoles from closely adjacent regions gave different configurations. With these facts in mind one would not expect rotation of the heart to influence the configuration of extrasystoles unless the amount of rotation were greater than the arc of a circle corresponding to the areas stimulated by Barker. Thus it would be expected that rotation of a few degrees would not influence the configuration of extrasystoles originating on the anterior surface of the right ventricle, whereas one would expect a change in configuration in extrasystoles arising from the left ventricle. The results of stimulation of points three and four on the right ventricle (in the presence of 30° rotation to the left on the horizontal axis), which were similar to those obtained by stimulating points one and two, show that the electrical axis of ventricular extrasystoles starting from the base of the right ventricle posteriorly is opposite to that of beats produced by electrical stimulation of a region near the apex of the anterior wall of the right ventricle.

DISCUSSION

It should be stated that a comparison of the electrocardiograms taken before operation and during the experiment failed to show any change in the QRS deflection in Lead I. In Lead III, in the instance of points one and two, QRS was more diphasic than in the control electrocardiogram, whereas the complex from point three was practically the same as the control before the stimulation, and inverted after the stimulation. Both before and after point four was stimulated, QRS in Lead III was inverted. This shifting of the QRS complex in Lead III was associated

with rotation of the cardiac apex up into the operative incision; the heart rotated about 30° on its horizontal axis at times during spells of rapid heart action (also during one short spell of paroxysmal ventricular tachycardia) and after the long pause following some extrasystoles, e.g., after stimulation of point three. In open-chest operations on dogs, as well as in humans, the heart likewise rotates about these two axes; this is independent of the individual heartbeat, but is probably related to the heart rate. We attribute the behavior to an increase in the amount of blood contained within the heart chambers at the end of the long pause following extrasystole, or to the accumulation of blood within the ventricular chambers due to inefficient emptying during tachycardia. We feel that in the case of point three this rotation of the heart on its horizontal axis occurred during the long pause following the extrasystole, and therefore did not complicate the electrocardiogram which was the result of stimulating that point, since the blood accumulation would take place after the extrasystole occurred. It might be repeated here that it is probably true that even if the heart had rotated up into the wound at the time the right ventricle was stimulated at point four, this amount of rotation would not have changed the configuration of the resultant electrocardiographic tracing. Upon study of the results of stimulation of these four points it is of interest to note that when only Leads I and III are observed, even though they are observed simultaneously, stimulation of point one gives a tracing which is indistinguishable from that obtained from point three, although the former originated in the left ventricle and the latter in the right ventricle; the only factor which they have in common is that they arose near the base of the ventricles, although this was from points at least six centimeters apart and separated by the septum. Similarly, point two cannot be distinguished electrocardiographically from point four, although they are located in the left and right ventricles, respectively. The only factor they have in common is that they were at about the same level near the apex of the heart. These observations tend to indicate that the site of origin of a ventricular extrasystole determines the configuration of the electrocardiogram according to its position in relation to the base or apex of the heart, not according to its location in one or the other ventricle. Likewise, in these observations it is shown that changing the point of stimulation from left to right on the ventricular surfaces does not determine the configuration of the electrocardiogram, since points one and two, respectively, are considerably to the left of points three and four, respectively, and yet the configurations are the same in the curves from points one and three as they are in those from points two and four.

REFERENCES

1. Barker, P. S., Macleod, A. G., and Alexander, J.: The Excitatory Process in the Exposed Human Heart, *AM. HEART J.* 5: 720, 1930.
2. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle Branch Block, *AM. HEART J.* 7: 305, 1932.

3. Marvin, H. M., and Oughterson, A. W.: The Form of Premature Beats Resulting From Direct Stimulation of the Human Ventricles, *AM. HEART J.* 7: 471, 1932.
4. Lundy, C. J., and Bacon, C. M.: Premature Left Ventricular Beats From Electrical Stimulation of the Exposed Human Heart, *Arch. Int. Med.* 52: 30, 1933.
5. Kountz, W. B., Prinzmetal, M., Pearson, E. F., Koenig, K. F., and Smith, J. R.: Effect of Position of the Heart on the Electrocardiogram, *AM. HEART J.* 10: 605, 1935.
6. Ackerman, W., and Katz, L. N.: Reversal in Direction of the QRS Complex of Experimental Right Bundle Branch Block and Changes in the Heart's Position, *AM. HEART J.* 8: 490, 1933.
7. Kissin, G., Ackerman, W., and Katz, L. V.: Effect of Heart Position on Electrocardiographic Appearance of Bundle Branch Block in Man, *Am. J. M. Sc.* 186: 721, 1933.
8. Nathanson, M. H.: Electrocardiographic Study of Movements of the Heart With Change in Posture, *Proc. Soc. Exper. Biol. & Med.* 28: 766, 1931.
9. Katz, L. N., and Ackerman, W.: The Effect of the Heart's Position on the Ekg Appearance of Ventricular Extrasystoles, *J. Clin. Investigation* 11: 1221, 1932; Kountz et al., loc. cit.
10. Fossier, A. E.: Mechanical Stimulation of Ventricular Extrasystoles in Man, *J. A. M. A.* 90: 1103, 1938.

A STUDY OF THE TRANSVERSE DIAMETER OF THE HEART SILHOUETTE WITH PREDICTION TABLE BASED ON THE TELEOROENTGENOGRAM*

HARRY E. UNGERLEIDER, M.D.,† AND CHARLES P. CLARK, M.D.‡
NEW YORK, N. Y.

SINCE Hodges and Eyster¹ described their formula for the estimation of the transverse cardiac diameter in man, many observers, notably Bainton² in America and Bedford and Treadgold³ in England, have endorsed the transverse cardiac diameter as the most reliable index of heart size for all practical purposes. Many organizations, such as the New York Heart Association,⁴ the American Heart Association,⁵ and the Association of Life Insurance Medical Directors,⁶ have similarly given their endorsements of this measurement of heart size. The original work of Hodges and Eyster was done on orthodiagrams, and many observers felt that with a simple correction the table could be adapted to teleoroentgenograms.

Dietlen,⁷ Hammer,⁸ and others have found an overestimation of 1 to 2.5 cm. in the transverse diameters of the heart on teleoroentgenograms when compared with those obtained by the orthodiagram.

Bedford and Treadgold suggest that teleoroentgenogram measurements should not be compared with orthodiagram measurements but that a different standard of normal size should be used for the method. Although they prefer the orthodiagram, claiming that the error in teleoroentgenography arises from difficulty in centering the patient accurately with reference to the film, in centering the tube accurately in relation to the heart, and in obtaining records always in the same phase of respiration, we have not encountered any such difficulty. On the contrary, we find it easier to train technicians to center the patient and tube and to take the films in midinspiration than to train physicians to make accurate orthodiagrams.

As a matter of fact, moving the tube either upward or downward or to the right or left a distance of 2½ inches makes very little difference in the final result with the teleoroentgenogram.

Our technique for making teleoroentgenograms is very simple. The standing position is used; the patient is placed directly in front of the plate holder, with his chin resting on its upper part. The dorsum of his hands are placed over his hips, which brings the scapulae away

*Read before the Association of Life Insurance Medical Directors of America, Oct. 20, 1938.

Received for publication October 13, 1938.

†Equitable Life Assurance Society.

‡Mutual Benefit Life Insurance Company.

from the thoracic cage and aligns his shoulders with the top of the plate holder. The tube is 6 feet from the subject, and the target is centered upon the spine at the level of the angle of the scapula. The exposure is made in one-thirtieth of a second, and the voltage is varied with the thickness of the chest. Care is always taken to see that the patient's face is turned neither to the left nor to the right, and emphasis is especially placed on having the ventral surface of the patient firmly opposed to the cassette or plate holder.

Since life insurance companies have adopted for general use the teleoroentgenogram in preference to the orthodiagram because the former also gives evidence of pulmonary disease if it is present, we have been experiencing increasing difficulty in applying the Hodges-Eyster formula. We have felt that our efforts to adapt this formula to teleoroentgenograms gave results which were not entirely consistent. Medical directors of other companies have had the same experience, and simultaneous applications for insurance to different companies have resulted in the issuance of policies with different premium ratings when identical films were furnished to all the companies concerned.

We have felt that the suggestion of Bedford and Treadgold was a good one—that new criteria, based on teleoroentgenograms, be established.

In a previous study,⁹ one of us reported that the circumferences of the chest and abdomen vary with the index $\frac{\text{body weight}}{\text{height}}$, or $\frac{w}{h}$.

In another study,¹⁰ it was suggested that a similar relationship might exist between the transverse diameter of the heart and the index $\frac{w}{h}$. Consequently, we felt that, since our applicants comprise a fairly representative sample of the population, including persons of all builds, ages, occupations, and social spheres, a study of their roentgenograms by means of this index would be desirable.

In the present study of the transverse diameter of the heart silhouette, we found that a similar relationship does actually exist between this diameter and the index $\frac{w}{h}$.

We have included in this study only the records of cases in which the systolic blood pressures fell between 110 and 145 mm. Hg and the diastolic pressures between 60 and 100 mm. Hg—a total of 1,460 cases. It is pertinent at this point to state that all the teleoroentgenograms used in this study were made under identical conditions in the Diagnostic Laboratory of the Equitable Life Assurance Society, according to the technique described above. We first determined for each subject, the height-weight index, $\frac{w \times 10}{h}$. The cards were then sorted

by indexes and for each index group the average transverse diameter of the heart was computed. The findings of this study are recorded in Table I. In column A the index $\frac{w \times 10}{h}$ is given; in column B, the number of cases falling within each index; and in column C, the average transverse diameter for each index.

TABLE I
A STUDY OF 1460 TELEOROENTGENOGRAMS
(INCLUDES ONLY CASES IN WHICH THE SYSTOLIC BLOOD PRESSURE RANGED BETWEEN 110 AND 145 MM. HG. AND THE DIASTOLIC BETWEEN 60 AND 100 MM. HG.)

A INDEX $\frac{w \times 10}{h}$	B CASES	C AVERAGE T.D. HEART (CM.)
15	1	10.4
16	4	10.8
17	12	11.0
18	32	11.7
19	61	11.8
20	88	12.3
21	118	12.3
22	179	12.8
23	188	13.1
24	198	13.3
25	142	13.7
26	159	14.0
27	97	14.0
28	75	14.2
29	38	14.5
30	28	14.7
31	24	15.1
32	6	14.9
33	7	15.0
34	1	13.8
35	2	14.4
Total 1,460		(Average for all cases 13.277 cm.)

We have plotted Chart 1 with each index and corresponding average transverse diameter indicated by a cross. (The height-weight index average was carried to the first decimal point. This explains the position of the crosses in our graph, which, as will be noted, do not fall exactly on the index as given in Table I.)

The shape of the curve indicated by the points plotted in Chart 1 is a parabola with the axis vertical. It occurred to us, therefore, that possibly the function $\frac{w}{hd^2}$, in which "w" represents the body weight, "h" body height, and "d," the transverse diameter of the heart, might be constant, and a simple calculation indicated that, as a matter of fact, the value of this function is constant and is approximately 14.0 for all values of the index.

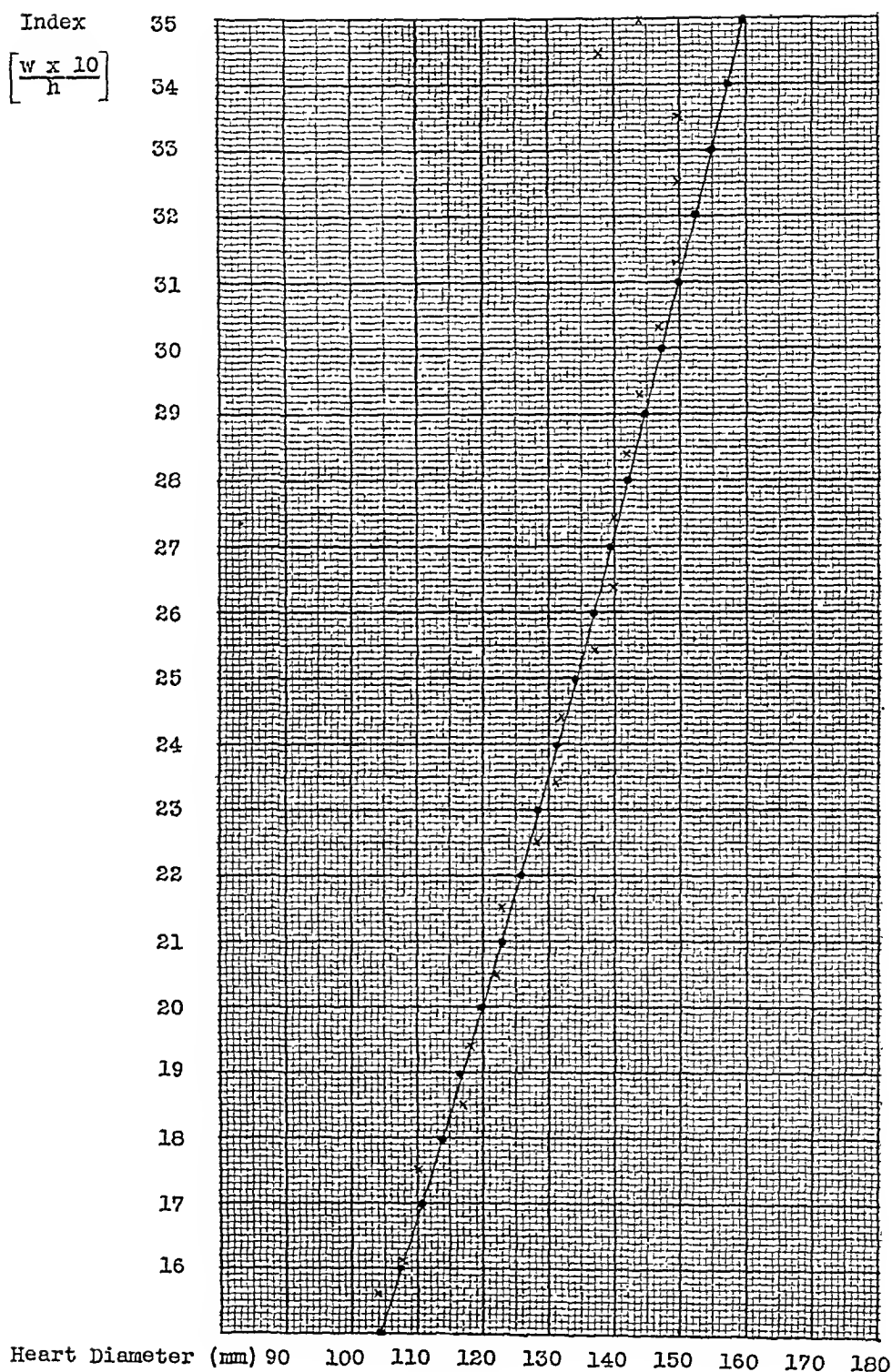


Chart 1.

TABLE II
THEORETICAL TRANSVERSE DIAMETERS OF HEART SILHOUETTE FOR
VARIOUS HEIGHTS AND WEIGHTS

TABLE FOR DETERMINING THE PER CENT
DEVIATION FROM AVERAGE

T.D. OF HEART	HEIGHT																			MINUS				AV. GE		PLUS					
	5'0"	1"	2"	3"	4"	5"	6"	7"	8"	9"	10"	11"	6'0"	1"	2"	3"	4"	5"	6"	25	20	15	10	5	5	10	15	20	25		
	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%		
100 mm.	83	85	86	87	89	90	92													75	80	85	90	95	100	105	110	115	120	125	
101 "	85	86	88	89	91	92	93	95												76	81	86	91	96	101	106	111	116	121	126	
102 "	87	88	90	91	92	94	95	97												77	82	87	92	97	102	107	112	117	122	128	
103 "	88	90	92	93	94	96	97	99	100											77	82	88	93	98	103	108	113	118	124	129	
104 "	90	92	93	95	96	98	99	101	102											78	83	88	94	99	104	109	114	120	125	131	
105 "	92	93	95	96	98	99	101	103	104	106										79	84	89	95	100	105	110	116	121	126	131	
106 "	94	95	97	98	100	101	103	104	106	108										80	85	90	95	101	106	111	117	122	127	133	
107 "	95	97	99	100	102	103	105	106	108	110	111									80	86	91	96	102	107	112	118	123	128	134	
108 "	97	99	100	102	104	105	107	108	110	112	113									81	86	92	97	103	108	113	119	124	130	135	
109 "	99	101	102	104	106	107	109	110	112	114	115	117								82	87	93	98	104	109	114	120	125	131	136	
110 "	101	102	104	106	108	109	111	113	114	116	118	119	121							83	88	94	99	105	110	116	121	127	132	138	
111 "	103	104	106	108	109	111	113	115	116	118	120	121	123	125						83	89	94	100	105	111	117	122	128	133	139	
112 "	105	106	108	110	111	113	115	117	118	120	122	124	125	127	129					84	90	95	101	106	112	118	123	129	134	140	
113 "	106	108	110	112	113	115	117	119	121	123	124	126	128	129	131	133				85	90	96	102	107	113	119	124	130	136	141	
114 "	108	110	112	114	115	117	119	121	123	125	126	128	130	132	133	135	137			86	91	97	103	108	114	120	125	131	137	143	
115 "	110	112	114	116	117	119	121	123	125	127	129	130	132	134	136	138	140	141		86	92	98	104	109	115	121	127	132	138	144	
116 "	112	114	116	118	120	121	123	125	127	129	131	133	134	136	138	140	142	144	146	87	93	99	104	110	116	122	128	133	139	145	
117 "	114	116	118	120	122	124	125	127	129	131	133	135	137	139	141	143	144	146	148	88	94	99	105	111	117	123	129	135	140	146	
118 "	116	118	120	122	124	126	128	129	131	133	135	137	139	141	143	145	147	149	151	89	94	100	106	112	118	124	130	136	142	148	
119 "	118	120	122	124	126	128	130	132	134	136	138	140	142	143	145	147	149	151	153	89	95	101	107	113	119	125	131	137	143	149	
120 "	120	122	124	126	128	130	132	134	136	138	140	142	144	146	148	150	152	154	156	90	96	102	108	114	120	126	132	138	144	150	
121 "	122	124	126	128	130	132	134	136	138	140	142	144	146	148	150	152	154	156	159	91	97	103	109	115	121	127	133	139	145	151	
122 "	124	126	128	130	132	134	136	138	140	143	145	147	149	151	153	155	157	159	161	92	98	104	110	116	122	128	134	140	146	153	
123 "	126	128	130	132	134	136	139	141	143	145	147	149	151	153	155	157	160	162	164	92	98	105	111	117	123	129	135	141	148	154	
124 "	128	130	132	134	137	139	141	143	145	147	149	152	154	156	158	160	162	164	166	93	99	105	112	118	124	130	136	143	149	155	
125 "	130	132	134	137	139	141	143	145	147	150	152	154	156	158	160	163	165	167	169	94	100	106	113	119	125	131	138	144	150	156	
126 "	132	134	137	139	141	143	145	148	150	152	154	156	159	161	163	165	167	170	172	95	101	107	113	120	126	132	139	145	151	158	
127 "	134	137	139	141	143	146	148	150	152	154	157	159	161	163	166	168	170	172	175	95	102	108	114	121	127	133	140	146	152	159	
128 "	136	139	141	143	146	148	150	152	155	157	159	161	164	166	168	171	173	175	177	96	102	109	115	122	128	134	141	147	154	160	
129 "	139	141	143	146	148	150	152	155	157	159	162	164	166	169	171	173	176	178	180	97	103	110	116	123	129	135	142	148	155	161	

Refer to paper entitled "A Study of the Transverse Diameter of the Heart Silhouette with Prediction Table Based on the Teleorontogram" presented to the Association of Life Insurance Medical Directors of America by Dr. Harry E. Ungerleider of the Equitable Life Assurance Society, and Dr. Charles P. Clark, of the Mutual Benefit Life Insurance Company. (1938.)

130	“	141	143	145	148	150	152	155	157	160	162	164	167	169	171	174	176	178	181	183	98	104	111	117	124	130	137	143	150	156	163
131	“	143	145	148	150	152	155	157	160	162	164	167	169	172	174	176	179	181	183	186	98	105	111	118	124	131	138	144	151	157	164
132	“	145	148	150	152	155	157	160	162	164	167	169	172	174	177	179	181	184	186	189	99	106	112	119	125	132	139	145	152	158	165
133	“	147	150	152	155	157	160	162	165	167	169	172	174	177	179	182	184	187	189	192	100	106	112	119	126	133	140	146	153	160	166
134	“	150	152	155	157	160	162	164	167	169	172	174	177	179	182	184	187	189	192	194	101	107	114	121	127	134	141	147	154	161	168
135	“	152	154	157	159	162	164	167	169	172	175	177	180	182	185	187	190	192	195	197	101	108	115	122	128	135	142	149	155	162	169
136	“	154	157	159	162	164	167	169	172	175	177	180	182	185	187	190	193	195	198	200	102	109	116	122	129	136	143	150	156	163	170
137	“	156	159	162	164	167	169	172	175	177	180	182	185	188	190	193	195	198	201	203	103	110	116	123	130	137	144	151	158	164	171
138	“	159	161	164	167	169	172	174	177	180	182	185	188	190	193	196	198	201	204	206	104	110	117	124	131	138	145	152	159	166	173
139	“	161	164	166	169	172	174	177	179	182	185	188	190	193	196	198	201	204	206	209	104	111	118	125	132	139	146	153	160	167	174
140	“	163	166	169	171	174	177	180	182	185	188	190	193	196	199	201	204	207	209	212	105	112	119	126	133	140	147	154	161	168	175
141	“	166	168	171	174	177	179	182	185	188	190	193	196	199	201	204	207	210	212	215	106	113	120	127	134	141	148	155	162	169	176
142	“	168	171	174	176	179	182	185	188	190	193	196	199	202	204	207	210	213	216	218	107	114	121	128	135	142	149	156	163	170	178
143	“	170	173	176	179	182	184	187	190	193	196	199	202	204	207	210	213	216	219	221	107	114	122	129	136	143	150	157	164	172	179
144	“	173	176	178	181	184	187	190	193	196	199	201	204	207	210	213	216	219	222	224	108	115	122	130	137	144	151	158	166	173	180
145	“	175	178	181	184	187	190	193	196	198	201	204	207	210	213	216	219	222	225	228	109	116	123	131	138	145	152	160	167	174	181
146	“	178	180	183	186	189	192	195	198	201	204	207	210	213	216	219	222	225	228	231	110	117	124	131	139	146	153	161	168	175	183
147	“	180	183	186	189	192	195	198	201	204	207	210	213	216	219	222	225	228	231	234	110	118	125	132	140	147	154	162	169	176	184
148	“	182	185	188	191	194	197	200	203	206	209	212	215	218	221	224	227	230	233	236	111	118	126	133	141	148	155	163	170	178	185
149	“	185	188	191	194	197	200	203	206	210	213	216	219	222	225	228	231	234	237	240	112	119	127	134	142	149	156	164	171	179	186
150	“	187	191	194	197	200	203	206	209	212	215	219	222	225	228	231	234	237	240	243	113	120	128	135	143	150	158	165	173	180	188
151	“	190	193	196	199	203	206	209	212	215	218	222	225	228	231	234	237	241	244	247	113	121	128	136	143	151	159	166	174	181	189
152	“	192	196	199	202	205	208	212	215	218	221	224	228	231	234	237	241	244	247	250	114	122	129	137	144	152	160	167	175	182	190
153	“	195	198	201	205	208	211	214	218	221	224	227	231	234	237	240	244	247	250	253	115	122	130	138	145	153	161	168	176	184	191
154	“	198	201	204	207	211	214	217	221	224	227	230	234	237	240	244	247	250	253	257	116	123	131	139	146	154	162	169	177	185	193
155	“	200	203	207	210	213	217	220	224	227	230	233	237	240	243	247	250	253	257	260	116	124	132	140	147	155	163	171	178	186	194
156	“	206	210	216	220	223	226	229	233	236	239	243	246	249	253	256	259	262	264	267	117	125	133	140	148	156	164	172	179	187	195
157	“	216	219	222	226	229	233	236	239	243	246	249	253	256	260	263	267	270	274	277	118	126	133	141	149	157	165	173	181	188	196
158	“			225	229	232	236	239	243	246	249	253	256	260	263	267	270	274	277	280	119	126	134	142	150	158	166	174	182	190	198
159	“					235	239	242	246	249	253	256	260	263	267	270	274	277	280	284	119	127	135	143	151	159	167	175	183	191	199
160	“						245	249	252	255	259	263	266	270	274	277	281	284	288	291	120	128	136	144	152	160	168	176	184	192	200
161	“								255	259	263	266	270	273	277	281	284	288	291	294	121	129	137	145	153	161	169	177	185	193	201
162	“								259	262	266	270	273	277	280	284	288	291	294	297	122	130	138	146	154	162	170	178	186	194	203
163	“										269	273	277	280	284	288	291	294	297	300	122	130	139	147	155	163	171	179	187	196	204
164	“										273	276	280	284	288	291	294	297	300	303	123	131	139	148	156	164	172	180	189	197	205

It appears, therefore, that a satisfactory evaluation of the crude data will be obtained by assuming the stated function to be constant. The actual value of the constant was determined in the following way:

$$\begin{aligned}\text{Average weight} &= 165.83 \text{ pounds} \\ \text{Average height} &= 68.04 \text{ inches} \\ \text{Average diameter} &= 132.77 \text{ mm.}\end{aligned}$$

(In order to obtain a constant with two digits, we multiplied the weight by 100,000.)

Our constant is, therefore,

$$\frac{w \times 100,000}{h(d)^2} = \frac{165.83 \times 100,000}{68.04 (132.77)^2} = 13.83$$

If men of different weights and heights were built in proportion to perfect cylinders, tables for all body circumferences and diameters could be constructed by the use of constants, e.g.,

$$\text{For diameters,} \quad C = \frac{w}{hd^2}$$

$$\text{or for circumferences, } C = \frac{w}{hc^2}$$

In a previous study, one of us found that the chest circumferences almost follow such constants, but the abdominal circumferences do not because of the fact that these circumferences are much affected by the amount of adipose tissue present. Therefore, our table for chest and abdominal circumferences was constructed by using the index $\frac{w}{h}$ in the manner shown in our original paper.

We have found, however, that the heart diameter so closely follows a constant, as is shown later, that such a constant can be used in the development of a table for heart diameters. On the other hand, the internal chest diameters do not follow such a constant, but more nearly follow a constant $\frac{\sqrt{wh}}{hd^2}$. Therein lies the chief fallacy in attempting to correlate heart diameters with the internal diameters of the chest.

With this value for our constant, we next proceeded to compute for each index included in Chart 1 the theoretical transverse diameter. These values are indicated by dots and connected by a solid line. It is evident that the curve thus produced represents a satisfactory graduation of the original data, and the constant thus found was accordingly adopted as suitable for the development of a table of standard diameters for all heights and weights.

By the use of this constant we next developed Table II, which gives the theoretical transverse diameters in millimeters for heights 5 ft. 0 in., to 6 ft. 6 in., inclusive, and for the weights commonly found for each height. It should be noted that in the original group of subjects the heights were taken in shoes, and the weights included all clothing

except coat and vest. The directions for use of the table are simple. Find in the table the height column corresponding to the height of the individual under consideration. Below, in that column, find the nearest weight. To the left on that line will be found in the first column the theoretical transverse diameter of the heart silhouette.

Our first problem in testing this table was to determine how closely the theoretical diameters corresponded at all points with the actual diameters found in the original material. In general, it may be stated that short men—those under the height of 68 inches—were found on the average to have diameters 1 to 2 mm. greater, and tall men—those over the height of 68 inches—1 to 2 mm. less than the theoretical. At no point in the table, however, does it appear that the deviation of actual from theoretical will average more than 1 or 2 per cent. We concluded, therefore, that it was unnecessary to make any correction for height.

The next problem was to determine whether, in the use of the table, any correction need be made for age. In Table III are recorded the results of this study. In column A, we find the age groups; in column B, the number of cases falling into each group; in column C, the total deviations (plus or minus, recorded separately) of actual transverse diameters from the predicted given in Table II; in column D, the difference between plus and minus deviations in column C; and in column E, those differences divided by the number of cases in the respective groups shown in column B.

TABLE III
EFFECT OF AGE ON TRANSVERSE DIAMETER OF HEART

A	B	C		D	E
AGE (YR.)	CASES	DEVIATIONS (MM.)		DIFFERENCE BETWEEN	CORRECTION FOR AGE (MM.)
		+	-	+ AND - IN	
				COL. C (MM.)	
15-29	123	514	501	+ 13	+0.1
30-39	293	1,185	1,294	-109	-0.4
40-49	571	2,544	2,261	+283	+0.5
50-59	358	2,118	1,441	+677	+1.9
60-70	115	661	510	+151	+1.3
Total	1,460				

It is obvious that no correction need be made for ages between 15 and 50 years. At later ages, the deviation from the theoretical is very slight, calling for only (approximately) a 1 per cent correction of the theoretical given in the table. Furthermore, such deviation as is shown in the above study (Table III) is probably the result of actual abnormality in a few cases included in the original material. It does not, therefore, appear necessary to make any correction for age.

Table IV gives the results of a study of the effect of blood pressure on the transverse diameter of the heart. This study was made on a

group of 2,192 subjects, all applicants for life insurance, but not necessarily accepted as insurance risks. In column A are noted the various blood pressure groups; in column B, the number of cases falling within each group; in column C, the total deviations (plus or minus, recorded separately) of actual transverse diameters from the predicted given in Table II; in column D, the difference between plus and minus deviations in column C; and in column E, those differences divided by the number of cases in the respective groups shown in column B.

TABLE IV

EFFECT OF BLOOD PRESSURE ON TRANSVERSE DIAMETER OF HEART (2,192 CASES)

A SYSTOLIC BLOOD PRESSURE (MM.)	B NUMBER OF CASES	C DEVIATIONS (MM.)		D DIFFERENCE BETWEEN + AND - IN COL. C (MM.)	E DIFFERENCE IN COL. D DIVIDED BY CASES IN COL. B (MM.)
		+	-		
109 and under	82	396	366	+ 30	+0.4
110-119	300	1,403	1,241	+162	+0.5
120-129	456	1,826	2,061	-235	-0.5
130-139	437	2,255	1,829	+426	+1.0
140-149	390	2,230	1,353	+877	+2.2
150-159	267	1,462	890	+572	+2.1
160-169	174	1,146	508	+638	+3.7
170-200	86	642	167	+475	+5.5
Total 2,192					

When the systolic blood pressure is below 130 mm. Hg the transverse cardiac diameter is normal. Above that level there is a slight though definite indication of increasing hypertrophy with increasing hypertension. It is worth noting, however, that this increase in the transverse diameter would not be noted by percussion, an observation made many years ago by Janeway in the study of essential hypertension.

As a final study of the original material we are including Chart 2, which pictures the distribution curve based on deviation by per cent of actual from theoretical diameters. The smoothed curve was kindly developed from the rough figures by Mr. Harry Jones and his assistants in the Mathematical Department of the Mutual Benefit Life Insurance Company.

With the idea that it might be helpful in determining at a glance the approximate percentage deviation of the actual from the theoretical transverse diameter, we have added to Table II a separate table showing the plus and minus deviations from the theoretical given in column 1 of the table. For example, if it is determined that, for the height and weight given, the theoretical diameter is 120 mm. and the actual is found to be 150 mm., one can consult the special table, and find the number 120 in the column giving 0 per cent deviation. In this line the number 150 is found in the column indicating

plus 25 per cent. Accordingly, the applicant's transverse diameter is 25 per cent over the predicted. The percentage of deviation for any diameter which does not fall within the columns represented can be

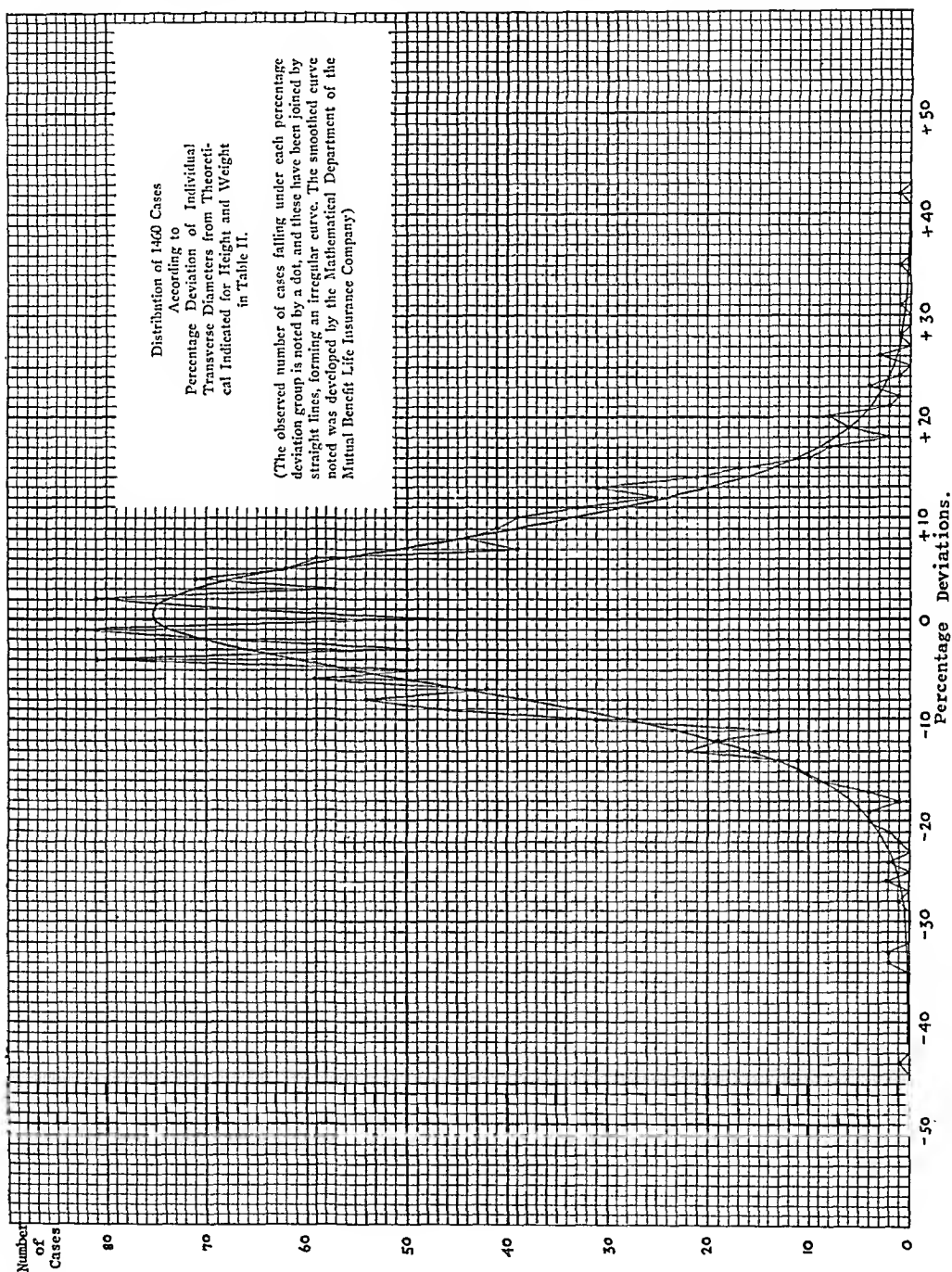


Chart 2.

approximated by reference to the two columns between which the observed falls.

It has generally been assumed that for the purpose of life insurance selection any heart diameter more than 10 per cent greater than the

average is to be regarded as indicative of hypertrophy of the heart. Pending future investigation of the actual effect on mortality of the deviation from average of the transverse diameter, it probably would be well in general to adhere to this figure. Nevertheless, we feel that judgment should be used in life insurance selection, since it is very certain that some hearts whose diameters are above 10 per cent of the expected are normal, just as others in which the heart diameter is distinctly less than the 10 per cent figure allowed are actually hypertrophied.

SUMMARY

A table was devised for obtaining the predicted transverse diameter of the heart silhouette based on the teleoroentgenogram.

The table is so constructed that it was found to be unnecessary to make any correction for excessive or subnormal height, or for age.

It would appear that when the systolic blood pressure is below 130 mm. the transverse diameter of the heart is normal. Above that level there is a slight or definite indication of increasing hypertrophy with increasing hypertension.

It is our opinion that, for the present, the predicted transverse diameter, plus 10 per cent, might be considered as the usual upper limit for the normal heart.

REFERENCES

1. Hodges, F. J., and Eyster, J. A. E.: Estimation of Transverse Cardiac Diameter in Man, *Arch. Int. Med.* 37: 707, 1926.
2. Bainton, J. H.: The Transverse Diameter of the Heart, *AM. HEART J.* 7: 331, 1932.
3. Bedford, D. E., and Treadgold, H. A.: The Size of the Healthy Heart and Its Measurement, *Lancet* 2: 836, 1931.
4. Nemet, Geza: Guide to Radiologic Diagnosis in Heart Disease, Heart Committee of the New York Tuberculosis and Health Association, Inc., 1931.
5. Criteria for the Classification and Diagnosis of Heart Disease, New York Tuberculosis and Health Association, Inc., 1932, p. 76.
6. Turner, Henry B., Nichols, Chas. F., and Ungerleider, Harry E.: A Recommended Standard for the Determination of Cardiac Enlargement: Transactions of the Association of Life Insurance Medical Directors, 1933, p. 184.
7. Dietlen, H.: Herz und Gefäße im Röntgenbild, Leipzig, 1923.
8. Hammer, G.: *Fortschr. a. d. Geb. Rönt.*, 1918, Vol. XXV, p. 510.
9. Clark, Chas. P.: The Chest and Abdominal Measurements as Related to Height and Weight With Presentation of Tables of Averages: Transactions of the Association of Life Insurance Medical Directors, 1929, Vol. XVI, p. 341.
10. Clark, Chas. P.: A Theoretical Study of Blood Pressure and Its Relation to Heart Size, Body Surface Area, and Metabolic Rate: Transactions of the Association of Life Insurance Medical Directors, 1933, Vol. XX, p. 224.

Department of Clinical Reports

THE EARLY RISE OF BLOOD PRESSURE IN CORONARY THROMBOSIS*

MORRIS M. WEISS, M.D.
LOUISVILLE, KY.

THE fall in blood pressure, both systolic and diastolic, which usually accompanies a coronary artery occlusion is one of the striking manifestations of the altered hemodynamics. This decrease in pressure is commonly mentioned as the most important of the criteria for differentiating it from an attack of angina pectoris, during which the blood pressure is frequently increased. While it has been observed that the pressure may not materially change during and after coronary occlusion, it is not sufficiently appreciated that the blood pressure may be higher than usual during the early painful phase of the attack. Thus, if a patient is seen in a prolonged attack of substernal pain with the blood pressure higher than it was when the patient was free of pain, a diagnosis of angina pectoris is often made and corresponding treatment administered.

A review of the literature reveals a paucity of observations as to the early rise of the blood pressure in coronary occlusion. Wood and Wolferth¹ anticipated the subject when they said: "The possibility presents itself that coronary occlusion produces an immediate rise of blood pressure in many cases, giving place to a subsequent fall at the time when these cases are usually seen by physicians. This explains the current belief that coronary occlusion and a drop in blood pressure are inseparable phenomena." They refer to a case of coronary occlusion reported by Fitz,² in which there was an accompanying rise of blood pressure. Barker³ states that the blood pressure in coronary thrombosis usually falls considerably within a few hours, though a brief initial rise may be observed.

The following case reports of coronary occlusion are illustrative of the frequent observation that an increase in blood pressure may occur soon after the onset of the occlusion.

REPORT OF CASES

T. W., a white woman 64 years old, had known for fifteen years that she had high blood pressure. After a coronary occlusion in January, 1935, her blood pressure, which had been as high as 200/110, ranged between 160/90 and 180/100. On

*From the Department of Medicine, University of Louisville.
Received for publication July 11, 1938.

July 19, 1935, she was seen in an attack of coronary occlusion, the pain of which had lasted two hours. The blood pressure was 176/94. Despite opiates the pain gradually became worse, and one hour later the pressure was 190/110. The next morning she was free of pain and the pressure was 126/70. During the succeeding weeks it was as low as 90/60. In the following year the blood pressure ranged from 136/80 to 172/90. On July 22, 1936, she had another coronary occlusion. The pressure, half an hour after the onset of pain, was 146/92. The pain became very severe and the pressure rose to 170/100. Four hours later, when no pain was present, the pressure was 116/68. During the next sixteen months her blood pressure was as low as 86/56 and as high as 150/90. On Nov. 22, 1937, she had still another occlusion. When seen at the height of the pain, two hours after the onset, the pressure was 180/100. Three hours later she had no pain and the pressure was 100/60. Thirty minutes later she died suddenly.

M. A., a white man 58 years old, had known for one year that his blood pressure was high. For six months he had been having attacks of angina pectoris, which was the reason he came to the hospital. During the evening of the eighteenth day after entering the hospital he had a coronary occlusion. On the morning of the attack his blood pressure was 164/104. He was seen fifteen minutes after the onset of the painful features of the occlusion, at which time the pressure was 210/112. Five minutes later it was 230/120. One hour later the pain had been relieved and the pressure was 176/112. The next day it was 150/104, but two days later it was 112/66. Convalescence was uneventful.

J. S., a white man 45 years old, whose blood pressure had always been within normal limits, was hospitalized because of attacks of angina pectoris occurring at rest. Three days after admission to the hospital he had a coronary occlusion. The blood pressure the previous day was 126/80. He was seen one hour after the onset of the pain. The blood pressure was now 150/100. Thirty minutes later, when he was free of pain and was quiet, the pressure was 116/80. He made an uneventful recovery.

DISCUSSION

If the blood pressure increases as a result of coronary occlusion, it does so during the early painful stages of the attack. At this time the patient is restless, anxious, conscious of his suffering, possibly fearful of death. These mental aspects, along with the pain and oppression of the occlusion, probably initiate pressor reflexes which cause the rise of the pressure. Pain alone is not responsible, for I have seen patients who died in a state of anginosis with a rapidly falling blood pressure. It is also probable that a temporary compensatory increase in peripheral vascular resistance occurs at the onset of a coronary occlusion as it does in an attack of left ventricular failure or in shock, elements of both of which are usually present in a coronary occlusion. However, in none of the cases cited above and in the majority of other cases of coronary occlusion in which we have observed an early rise in pressure were there clinical signs of paroxysmal dyspnea, acute pulmonary stasis, or pulmonary hypertension. Fishberg⁴ believes that shock or peripheral circulatory failure predominates in the first days of coronary thrombosis in individuals who have previously had slight or no symptoms of cardiac insufficiency. He comments on the observation that in the initial stage of traumatic shock the arterial pressure may rise, as a

consequence of arteriolar constriction in the extremities, before the fall. Mendlowitz, et al.,⁵ found, in closed chest experiments following sudden ligation of the anterior descending branch of the left coronary artery in dogs, relatively insignificant immediate changes in the pressure. They thought this suggested that, for at least a short period following the coronary occlusion, a peripheral vasoconstriction occurred to compensate for the coincident diminution in cardiac output.

CONCLUSION

The blood pressure frequently rises during the early painful stages of coronary occlusion. This should not be confused with the increase in pressure which often accompanies an attack of angina pectoris.

REFERENCES

1. Wood, F. C., and Wolferth, C. C.: Angina Pectoris. The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison With Effects of Experimental Temporary Coronary Occlusion, *Arch. Int. Med.* 47: 339, 1931.
2. Fitz, R.: A Case of Angina Pectoris With Cardiac Infarct Induced by the Intravenous Injection of Sodium Tetra-Iodophenolphthalein, and Followed by Relief of Anginoid Symptoms, *Tr. A. Am. Physicians* 43: 292, 1928.
3. Barker, L. F.: Contemporary Views of Angina Pectoris and of Coronary Thrombosis, *New York State J. Med.* 35: 408, 1935.
4. Fishberg, A. M.: Heart Failure, p. 613, Philadelphia, 1937, Lea & Febiger.
5. Mendlowitz, M., Schauer, G., and Gross, L. F.: Hemodynamic Studies in Experimental Coronary Occlusion. II. Closed Chest Experiments, *AM. HEART J.* 13: 664, 1937.

SPONTANEOUS RUPTURE OF A PAPILLARY MUSCLE OF THE HEART

REPORT OF CASE*

V. MORAGUES, M.D.

St. Louis, Mo.

THE spontaneous rupture of a papillary muscle of the heart is so rare that it has been referred to as a medical curiosity.¹ Many books on cardiology do not mention it. As pointed out by Stevenson and Turner,² there were two cases in 6,000 autopsies at the Baltimore City Hospital, none in 14,000 autopsies at the Johns Hopkins Hospital, and none in 2,000 autopsies at the University of Maryland Hospital. The present is the only case in 3,400 autopsies at the St. Louis University group of hospitals.

A review of the literature shows that only twenty-one cases have been reported. In 1935 Stevenson and Turner² reported one case and reviewed the literature up to that time. Nineteen cases had been reported and could be classified as follows: two cases of ruptured papillary muscle in the right ventricle, one case in which both papillary muscles in the left ventricle were broken, ten cases in which the left posterior papillary muscle was broken, and two cases in which the left anterior papillary muscle was broken; in four cases it was not stated which muscle was ruptured. In the case of Stevenson and Turner an anterior papillary muscle of the left ventricle was broken. In 1937 Payne and Hardy³ reported a case of traumatic rupture of both papillary muscles in the left ventricle. Ours is another case of broken anterior papillary muscle of the left ventricle, the fourth to be published.

In most of the cases the rupture was caused by atherosclerosis of the coronary arteries with thrombosis and infarction of the myocardium. One resulted from syphilis,⁴ one in the right ventricle from tuberculosis, another in the right ventricle from puerperal sepsis, and one from trauma.³ Traumatic rupture of a papillary muscle is rather rare, although somewhat more frequent than spontaneous rupture. Some papers on traumas of the heart⁵ do not include this condition.

The clinical picture in most of the cases is that of acute coronary thrombosis, and, when the muscle breaks, acute mitral insufficiency with pulmonary edema. In no case has the diagnosis of broken papillary muscle been made during life, but in the case of Wankel⁶ the acute mitral insufficiency was recognized clinically. In our records there is a case in which the diagnosis of traumatic rupture of the chordae tendineae of

*From the Department of Pathology, St. Louis University School of Medicine.
Received for publication July 14, 1938.

the mitral valve was made by Dr. R. A. Kinsella about a year before death. The autopsy verified the diagnosis. The present discussion, however, is limited to rupture of the papillary muscles. In several cases a loud systolic murmur was heard at the apex of the heart, while in other cases it was a to-and-fro whistling murmur. In a few of the cases the patient stated that something had torn in his chest or heart. Most of the patients died suddenly, but a few survived for several months after the rupture.

Fig. 1.



Fig. 2.

Fig. 1.—Broken anterior papillary muscle of the left ventricle. Fibrosis of myocardium.

Fig. 2.—Broken anterior papillary muscle of the left ventricle. Marked atherosclerosis of aorta.

CASE REPORT

A. S., a 52-year-old white man, had been known to have hypertension for at least ten years, the systolic blood pressure oscillating between 200 and 210. No signs of heart failure had been presented, nor had any murmurs been heard on auscultation.

The patient had drunk some beer the day before his death. On the day of his death he lapsed suddenly into unconsciousness after lunch and was seized with convulsions. When he recovered consciousness he complained of fullness in his chest,

Fig. 3.

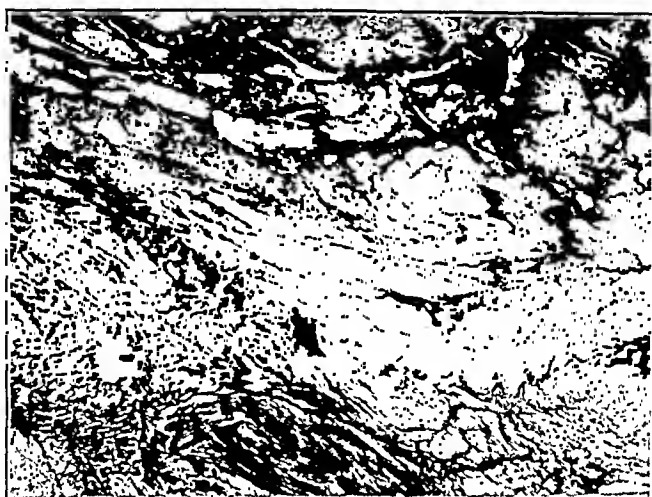


Fig. 4.



Fig. 5.

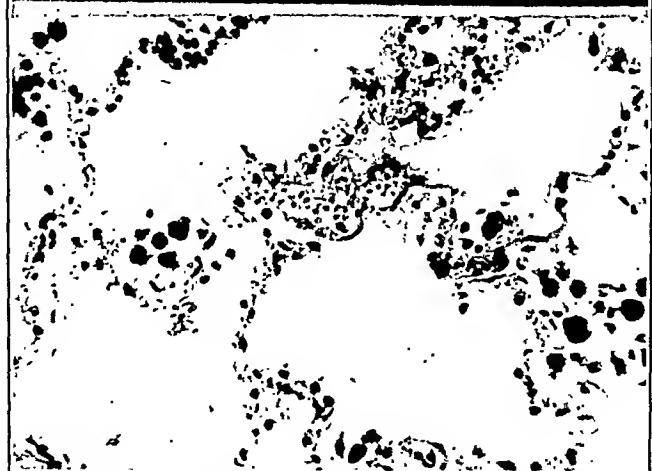


Fig. 3.—Marked fibrosis and necrosis of myocardium (Mallory stain).

Fig. 4.—Extreme atherosclerosis of aorta (hematoxylin and eosin).

Fig. 5.—Edema of the lungs, alveoli filled up with albuminous fluid, many heart-failure cells.

mainly in the precordial region. He remarked that his lungs were filling up and that he could not breathe. He was taken to the hospital, but died on the way.

Autopsy Findings.—The body was that of a well-developed and well-nourished white man approximately 50 years of age. The lips were markedly cyanotic. The jugular veins were very prominent and much engorged. The chest was broad and symmetrical. A very slight degree of edema was present over the ankles and the inner aspects of both thighs. There were about 50 c.c. of a thin, yellowish fluid in the right pleural cavity.

The heart was moderately enlarged, mainly due to enlargement of the left ventricle. The epicardium was quite smooth, thin, and intact. On examination of the heart before dissection, a soft area was found on the anterior wall of the left ventricle. On cut section this soft area was pale and thin, and was surrounded by an area of marked fibrosis. The anterior papillary muscle of the left ventricle was broken at a point about two-thirds of the distance from its origin to the point of insertion of the chordae tendinae. The torn edges were ragged and necrotic (Fig. 1). The base of this papillary muscle was in the center of the softened area mentioned above. The leaflet of the mitral valve normally attached to this muscle was freely movable in both directions and the valve must have been markedly incompetent. There was a marked degree of atherosclerosis in the proximal part of the aorta, mainly around the coronary openings (Fig. 2). The coronary arteries were tortuous, thick, and sclerotic; the anterior descending branch of the left coronary was completely occluded by an organizing thrombus.

The lungs showed an extreme degree of edema, were distended, and were heavier than normal. On cut section a large amount of serous, frothy fluid oozed from the parenchyma and the bronchi. Hypostatic congestion was also present. Both lungs were markedly anthracotic. The remaining viscera showed nothing but edema and congestion.

Microscopic Examination.—Sections of the heart taken from the infarcted area showed marked fragmentation and segmentation of the muscle fibers with some necrosis, lack of striation, pronounced fibrosis, and some areas of hemorrhage. The intima of the coronary vessels was markedly thickened with fibrous tissue. The aorta showed extreme thickening of the intima with fibrous tissue and deposits of lipid material (Fig. 4). The media showed some edema, necrosis, and infiltration with lymphocytes and monocytes. The lungs presented very marked edema, an albuminous fluid filling most of the alveoli. There was also considerable congestion throughout the section, with many pigment-loaded phagocytes (heart-failure cells) (Fig. 5). A moderate amount of anthracotic pigment was present.

DISCUSSION

The interpretation of this case is rather simple. The sequence was: atherosclerosis of the coronary arteries with thrombosis of the descending branch of the left coronary, infarction of the anterior wall of the left ventricle, spontaneous rupture of the anterior papillary muscle of the left ventricle causing sudden insufficiency of the mitral valve, and acute pulmonary edema.

The cause of this acute pulmonary edema, we believe, is mechanical, and is due to the acute mitral insufficiency. Prior to this there had undoubtedly been weakening of the left ventricular muscle due to the infarction of the anterior wall of the ventricle.

It is well known that acute pulmonary edema can be produced experimentally in dogs and rabbits by ligating the aorta, by necrotizing the wall

of the left ventricle (with alcohol or 5 per cent silver nitrate), or by ligating three-fourths of the pulmonary veins.^{7, 8}

Our case was one of sudden failure of the mitral valve and necrosis of the wall of the left ventricle.

Of the previously published cases, only in that of Wankel did acute pulmonary edema develop. It is an interesting fact that in Wankel's case it was also the anterior papillary muscle of the left ventricle which ruptured.

SUMMARY

This is the report of a case of very marked atherosclerosis of the coronary arteries, thrombosis of the anterior descending branch of the left coronary, infarction of the myocardium in the anterior wall of the left ventricle, spontaneous rupture of the left anterior papillary muscle, acute pulmonary edema, and sudden death.

REFERENCES

1. Levy, R. L.: *Disease of the Coronary Arteries and Cardiac Pain*, New York, 1936, The Macmillan Company.
2. Stevenson, R. R., and Turner, W. J.: Rupture of a Papillary Muscle in the Heart as a Cause of Sudden Death, *Bull. Johns Hopkins Hosp.* 57: 235, 1935.
3. Payne, W. C., and Hardy, H. H.: Traumatic Rupture of Papillary Muscles of Mitral Valve, Case, *New Orleans M. & S. J.* 89: 373, 1937.
4. Spalding, E. D., and Van Glahn, W. C.: Syphilitic Rupture of a Papillary Muscle of the Heart, *Bull. Johns Hopkins Hosp.* 32: 30, 1921.
5. Barber, Hugh: Trauma of the Heart, *Brit. M. J.* 1: 433, 1938.
6. Wankel: Ein Fall von spontaner Papillarmuskelzerreissung, Dissertation, Gies-sen, 1911.
7. Coelho, E., and Rocheta, J.: Etudes expérimentales sur la pathogenie de l'œdème aigu du poumon, *Ann. Med.* 34: 91, 1933.
8. Cataldi, G. M.: Ricerche sperimentali sulla patogenesi dell' edema acuto del polmone, *Policlinico* 44: 170, 1937.

ARTERIAL THROMBOSIS FOLLOWING SIMPLE CONTUSION*

REPORT OF A CASE

FAY A. LEFEVRE, M.D.

CLEVELAND, OHIO

IN A clinic devoted to the study of vascular disease, the major portion of cases of thrombosis and embolism are secondary to disease of the heart or peripheral arteries in older persons. It is well known, of course, that arterial thrombosis may occur following trauma, but actual experience, as a rule, does not disclose many cases of this type. Arterial thrombosis following fracture of an extremity, and deep wounds which necessitate ligation of one or more large vessels are seen from time to time, but thrombosis resulting from a simple contusion is of sufficient rarity and interest to be worth recording.

The case of this type to be presented is instructive both from the standpoints of diagnosis and of treatment, for the history furnished evidence that thrombosis following a minor accident may be easily overlooked, and an unusual opportunity was offered to observe and evaluate the results of treatment in a young, healthy patient whose circulatory system was normal except for that portion of it affected by the injury.

CASE REPORT

The patient, a white boy, aged 16 years, reported to the Vascular Clinic of St. Luke's Hospital on Feb. 5, 1938. His complaint was that he had had pain in the right leg for six months, that is, since August, 1937. At that time, while acting as a caddy, he had been struck in the right calf by a golf ball. The ball had been driven from the preceding tee, and had struck him a direct blow; it had traveled about a hundred yards in the air before striking him. After the accident he was able to continue with his work throughout the day and, except for local pain and tenderness, experienced no unusual symptoms. The skin was not broken, but for a period of a week there was a definite area of ecchymosis.

Several days following the accident he noticed that it was difficult for him to walk without resting. He observed that his right leg tired more easily than the left, and after walking moderate distances he would frequently have slight pain in the right calf. It was always his observation that this pain was relieved by rest. He also had noticed that the right leg was usually colder than the left, and frequently appeared paler. In spite of the pain in the leg he was able to carry on his work as a caddy during the remainder of the golf season.

About two months after the accident his condition became much worse. He was able to walk only three or four blocks at a slow pace before the pain in the right leg developed. From November, 1937, until the time of his admission to the Clinic, there had been a gradual decrease in the distance he could walk until finally pain appeared after walking only about one block. He was attending school and found it impossible to participate in any athletic competition. At no time had he experienced pain when at rest.

*Vascular Clinic, St. Luke's Hospital, Cleveland, Ohio.

Received for publication July 16, 1938.

In the period of six months that had elapsed since the accident, during which the symptoms had become increasingly severe, the patient had consulted several physicians who had offered various diagnoses, such as arthritis, neuritis, and rheumatism, and had prescribed aspirin and other treatment without the slightest effect. No investigation of circulatory function had been made by anyone.

Except for the injury and its sequelae, nothing in the patient's past history was pertinent to the condition from which he sought relief. He had never had scarlet fever or diphtheria, his feet had never been exposed to cold weather, there was no history or evidence of diabetes, and he did not smoke.

A general physical examination and special examinations of the eyes, ears, nose, and throat showed no abnormalities, and all of the peripheral reflexes were normal.

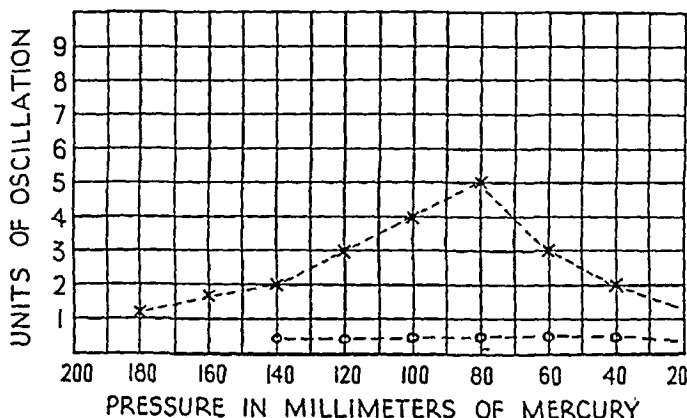


Fig. 1.—Oscillometric readings in both legs before treatment. (X, left leg; O, right leg.)

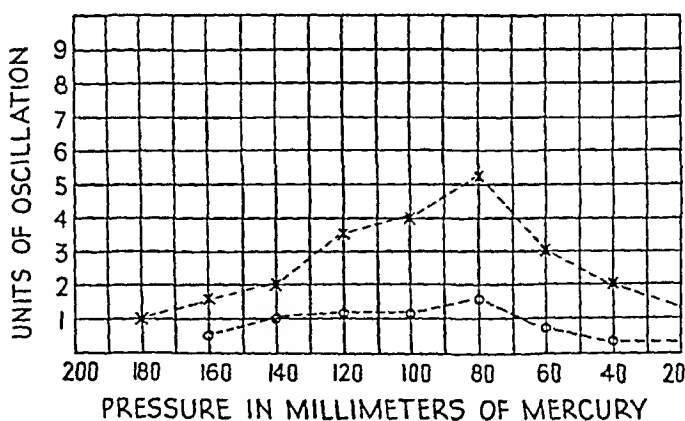


Fig. 2.—Oscillometric readings in both legs after passive vascular exercise (pavaex) treatment for sixty-five hours. (X, left leg; O, right leg.)

The patient was 5 feet, 6 inches tall, weighed 135 pounds, and appeared well developed and well nourished. The blood pressure was 110/70, and the pulse rate 72. Routine examinations of the blood and urine yielded normal findings, and the blood Wassermann reaction was negative.

Examination of the lower extremities revealed slight atrophy of the right calf muscles. Actual measurements indicated a difference of 3 cm. in circumference between the right and left legs. The right leg appeared to be paler than the left, in the horizontal position. On elevation, both feet and legs appeared pale. The pallor of the left leg was less marked than that of the right. In the dependent position the right leg showed a marked rubor, whereas the left leg was of a normal pink color. After exposure to room conditions the temperature of the right great

toe was 28° C. and of the left great toe, 32° C. There were no localized areas of tenderness. The femoral pulsations on both sides were normal. The popliteal, posterior tibial, and dorsalis pedis pulses were absent on the right side, but of good quality on the left. There was no edema, ulceration, or varicose veins. Oscillometric studies indicated good pulsation in both thighs. The pulse of the left leg and foot was normal, and the pulse of the right leg and foot was greatly diminished (Fig. 1). Intracutaneous histamine tests indicated a normal capillary response in both legs.

From the history and physical findings it was apparent that the patient was suffering from thrombosis of the posterior tibial artery, which probably was secondary to the injury suffered six months previously. Passive vascular exercise (pavaex) was instituted in an effort to establish an increase in the collateral circulation. From February 7 until June 4 the patient received this treatment for a total of sixty-five hours. No other form of treatment was administered during this period. The treatment was applied from one and one-half to two hours at a time, three times a week. More intensive therapy was not possible because the patient wished to remain in school.

During this period considerable subjective improvement was noted. The walking distance gradually increased and the degree of pain was considerably less. After the sixty-five hours of treatment the patient could walk about seven blocks without pain, as contrasted with one block when he was first examined. Improvement in the circulation was shown objectively, also, for the oscillometer recorded an increase from one-half to one and one-half units (Fig. 2). The temperature of the right foot was still lower than that of the left, but this was not noticeable to the patient. The temperature of the right great toe had risen from 28° C. to 30° C.

COMMENT

In many cases of thrombosis and embolism of the peripheral arterial system there is evidence that adequate collateral circulation develops spontaneously. For this reason it is often difficult to decide whether the treatment instituted early in the course of the circulatory disturbance is really responsible for improvement. In this instance, however, adequate time had elapsed since the occurrence of the injury to allow collateral circulation to increase spontaneously, if it were going to do so. Since, instead of any improvement, the patient's condition had become progressively worse before he presented himself at the clinic, and since after treatment was instituted he displayed marked betterment, it seems justifiable to conclude, in this case, that the passive vascular exercise (pavaex) treatment was responsible for the increase in circulation in the extremity.

During the summer vacation it will be possible for the patient to report more often for treatments, which are to be continued at least until they have been administered for a minimum of 100 hours. It is expected, in view of the patient's initial response, that additional improvement will result with continuation of this therapy.

AURICULAR FLUTTER AND COMPLETE HEART BLOCK

N. J. DIGREGORIO, M.D., AND J. HAMILTON CRAWFORD, M.D.*
BROOKLYN, N. Y.

WHEREAS auricular flutter and complete heart block are individually comparatively common, an association of the two conditions is unusual. The first accurate description of a combination of these disturbances in rhythm, with electrocardiographic proof, was reported by Jolly and Ritchie,¹ in 1911. Recently, Jourdonais and Mosenthal² described a case and thoroughly reviewed the literature; they found twenty-nine authentic cases, including their own. The details of these cases can be found in this article,² hence it is unnecessary to recapitulate them. The rarity of the condition is further emphasized by the fact that Willius³ encountered it only once in the electrocardiograms of 40,000 patients, while at Kings County Hospital it has been observed only twice in over 20,000 records. The following report, which adds two more to the reported cases, gives a summary of the findings in these two cases.

REPORT OF CASES

CASE 1.—M. R., a white man, 61 years of age, was admitted to Kings County Hospital for the first time on Nov. 1, 1935, complaining of shortness of breath, pain in the chest on exertion, cough, and swelling of the legs, all of seven months' duration; these symptoms had become more severe four weeks before admission. Neither his past nor family history was significant. Physical examination showed a large, well-nourished white man, sitting up in bed, orthopneic and cyanotic. The neck veins were distended as far as the angle of the jaw. The pulse was irregular, and the rate was 100 beats per minute. The blood pressure was 150/90. The vessels revealed a moderate degree of sclerosis. The apex beat was located outside the midclavicular line, 13 cm. from the midsternal line. There was a loud, blowing systolic murmur at the apex and a short rough systolic at the aortic area. Moist râles were heard at the bases of both lungs posteriorly. The edge of the liver was palpable three fingerbreadths below the costal margin and there was evidence of a small amount of free fluid in the abdominal cavity. The extremities showed slight edema. The blood sugar was 330 mg. per 100 c.c. A teleoroentgenogram of the chest showed a marked increase in the transverse diameter of the heart; the cardiothoracic index was 0.65. The electrocardiogram revealed auricular flutter at a rate of 250, with a varying block producing a ventricular rate of 100 (Fig. 1 A). Digitalis was ineffective in changing the rhythm but slowed the ventricular rate to about 60 beats per minute. The patient was discharged two weeks later, greatly improved; his diabetes was controlled without using insulin. The diagnosis was arteriosclerotic heart disease, and auricular flutter.

The patient was admitted to the hospital for the second time on June 23, 1936, having attended the cardiac clinic from time to time. Although digitalis was prescribed by the clinic physicians, he took it only occasionally—approximately one tablet a day for a few weeks and none for several weeks at a time. For at least

*From the Department of Medicine, Long Island College of Medicine, and the Department of Cardiology, Kings County Hospital.

Received for publication July 20, 1938.

two weeks before admission he had taken no digitalis or any other drug. On admission he had essentially the same complaints as previously, namely, dyspnea, precordial pain on exertion, and swelling of the legs and abdomen. The most important physical findings were orthopnea, cyanosis, distention of the neck veins, and rapid venous pulsations at the base of the neck. The blood pressure was 180/110. The pulse was slow (40 per minute) and regular.

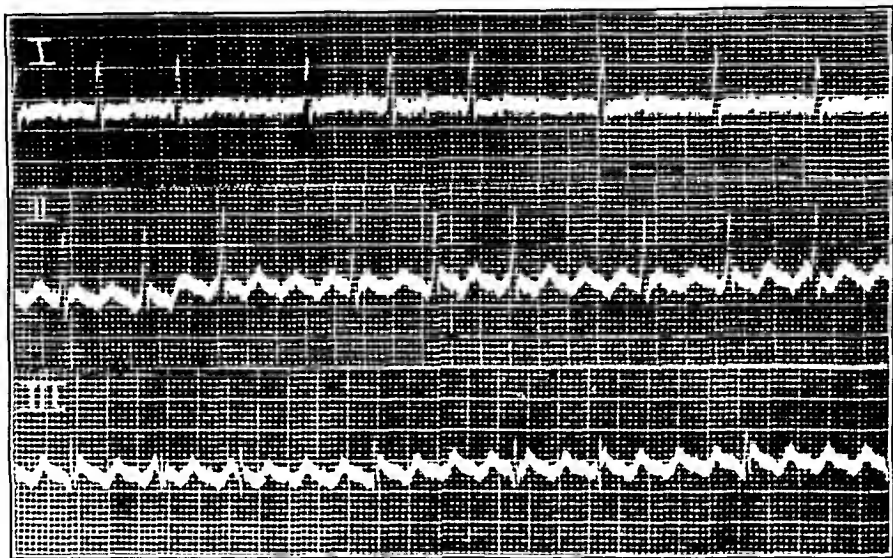


Fig. 14.—Case 1. Auricular flutter with irregularity of the ventricle (Nov. 16, 1935).

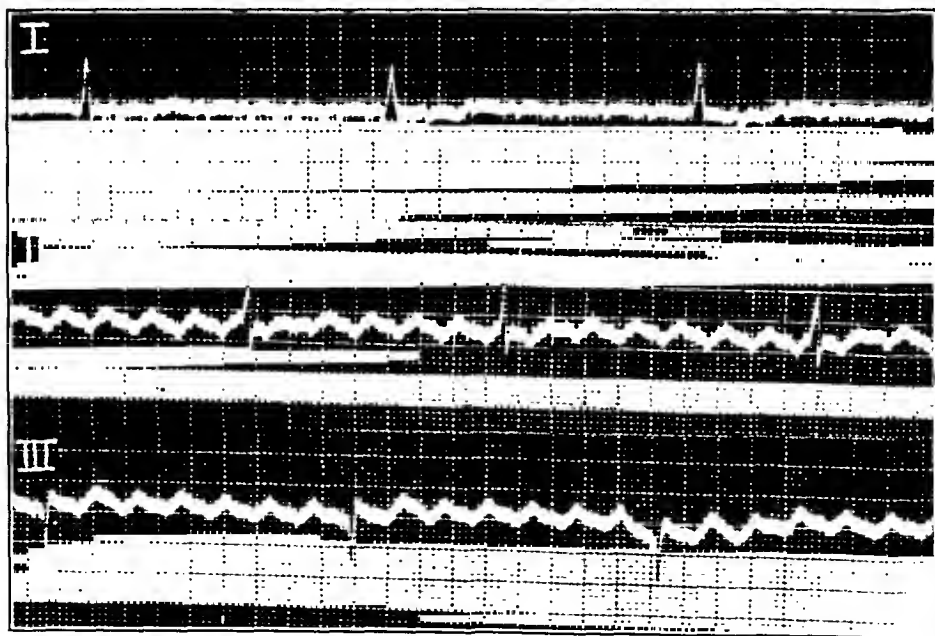


Fig. 1B.—Case 1. Auricular flutter with complete heart block (June 26, 1936).

The cardiac findings were the same as on the previous admission. There were moist râles at the bases of both lungs, enlargement of the liver, ascites, and edema of the legs. The electrocardiogram revealed auricular flutter at a rate of 214 and complete heart block with a ventricular rate of 33 (Fig. 1 B). He was again com-

pletely digitalized, and large doses of quinidine sulfate were given; both, however, were ineffective in changing either the rate or the rhythm.

Subsequently, he was readmitted to the hospital three times before his death in November, 1937. On each occasion he had essentially the same complaints and physical findings and a heart rate which varied between 30 and 40. The anasarca was most resistant to any form of treatment, including complete digitalization, ammonium chloride, and mercurpurin; both intravenously and in the form of suppositories. Numerous electrocardiograms all showed auricular flutter and complete auriculoventricular block.

CASE 2.—C. E., a white man, 62 years old, was admitted to Kings County Hospital on March 23, 1936, complaining of precordial pain and dyspnea. The family and past personal histories contributed nothing of significance. The patient was well until ten days before admission, when, while walking, he was seized with sudden severe substernal pain which caused him to fall to the ground and become dyspneic. Thereafter, he had had attacks of substernal pain on the slightest exertion.

Physical examination showed a white man lying quietly in bed, in no apparent discomfort. The important physical findings were a rapid regular pulse of 110, and a blood pressure of 140/100. The heart was slightly enlarged, the apex being situated just outside the midclavicular line. There were a few moist râles at the

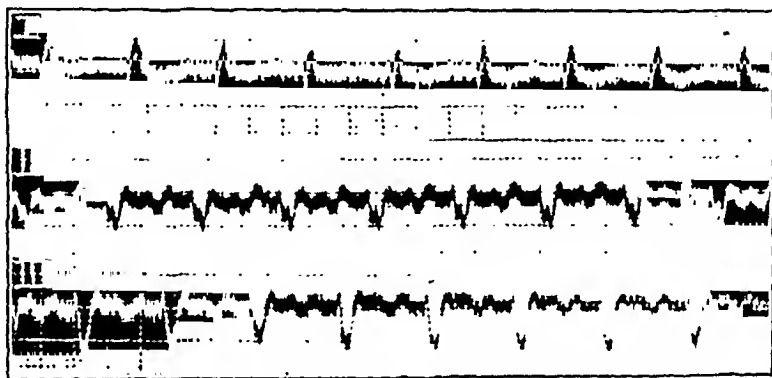


Fig. 2A.—Case 2. Sinus rhythm with intraventricular conduction disturbance and left axis deviation (March 25, 1936).

bases of the lungs. The laboratory data were negative. The electrocardiogram showed normal sinus rhythm at a rate of 110, left axis deviation, and intraventricular conduction disturbance (Fig. 2 A). A question which arises with respect to this record is whether the rhythm is normal sinus rhythm or auricular flutter. Leads II and III suggest the latter possibility, but on close analysis the timing of the peaks of the different waves does not appear to conform to that seen in auricular flutter. One concludes, therefore, that the rhythm is of sinus origin. Although the tracing does not show the typical features of acute coronary occlusion, in view of the history and the fact that there is a pronounced disturbance of intraventricular conduction (which frequently masks the characteristic findings of coronary thrombosis) a diagnosis of coronary occlusion was made. The patient was discharged from the hospital considerably improved, and directed to take $1\frac{1}{2}$ grains of digitalis per day.

He remained well until September, 1936, when he was readmitted, complaining of shortness of breath on exertion and swelling of the legs and abdomen, of two weeks' duration. Physical examination showed an acutely ill individual, orthopneic and cyanotic, with distended neck veins. The pulse rate was slow (24 per minute) and regular, and the blood pressure was 180/100. The heart was tremendously enlarged, the apex being in the anterior axillary line; the heart sounds were distant. Moist râles were heard at the bases of both lungs, and the liver extended three

fingerbreadths below the costal margin. Ascites and edema of the extremities were present. Except for a trace of albumin in the urine the laboratory findings were normal. The electrocardiogram (Fig. 2 B) showed auricular flutter at a rate of 214, complete heart block with a ventricular rate of 33, left axis deviation, and left bundle branch block. During the first few days in the hospital repeated Stokes-Adams attacks occurred; they were controlled by ephedrine and gradually disappeared. The patient was discharged at the end of three months in good condition, with no ascites or edema. The diagnosis was hypertensive and arteriosclerotic heart disease, auricular flutter, and complete heart block.

He re-entered the hospital in February, 1937, with practically the same complaints and physical findings as on the previous admission. The electrocardiogram again showed auricular flutter at a rate of 231, complete heart block with a ventricular rate of 30, left axis deviation, and an intraventricular conduction disturbance. He grew worse progressively, and died three days after admission.

On post-mortem examination the classical features of heart failure, including pulmonary edema, hydrothorax, ascites, and anasarca, were found. The heart

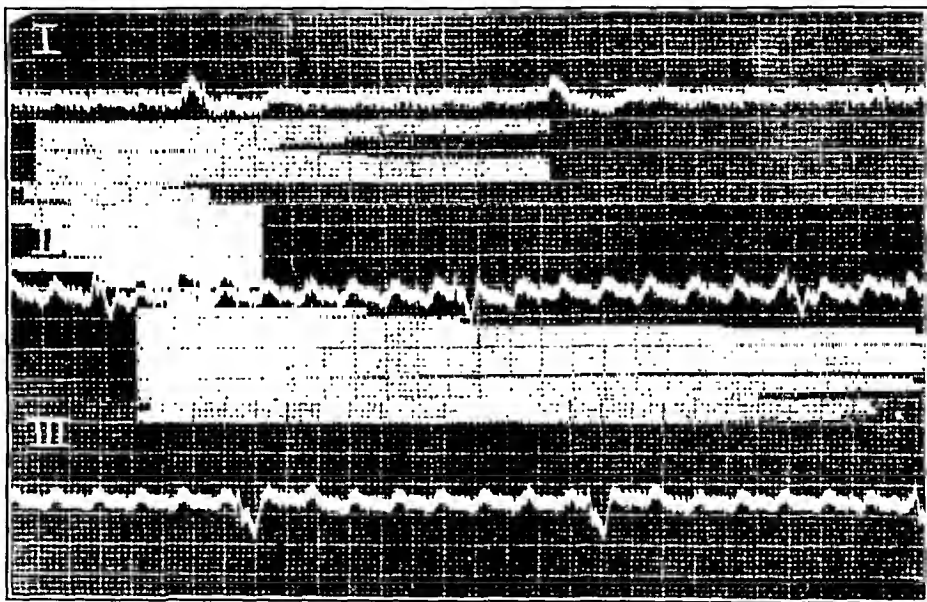


Fig. 2B.—Case 2. Auricular flutter, complete heart block, and left bundle branch block (Oct. 1, 1936).

weighed 800 gm.; the valves appeared normal and the main branches of the coronary arteries were patent. The myocardium showed a small amount of interstitial fibrosis and at the upper end of the interventricular septum there was an area of fibrosis measuring about 1 cm. in diameter. This undoubtedly was an old healed myocardial infarct involving the bundle of His, as had been suspected when he first came to the hospital.

DISCUSSION

The rarity of the association of auricular flutter and complete heart block has been alluded to already. Of the reported cases only four of the thirty-one, including the two reported in this paper, occurred in women. The age incidence varied from 13 to 74 years, with 80 per cent occurring in patients more than 50 years of age. This is to be expected, as a study of the etiology reveals that the condition takes place almost

exclusively in patients suffering from arteriosclerosis, hypertension, and coronary artery disease. There were only three cases of syphilitic heart disease, and one each of rheumatic, congenital, and thyreotoxic heart disease. Jourdonais and Mosenthal² have classified the previous cases into different groups, i.e., those in which the combination developed after the administration of drugs but in which one or the other disturbance of rhythm was present before medication was given, and those in which auricular flutter and heart block occurred spontaneously. In the majority of cases the disturbances appear spontaneously, but in a patient who is receiving digitalis, the possibility that it may be the cause must be seriously considered and the drug withdrawn in the hope that the abnormal rhythm will disappear. Neither of our patients had complete heart block when first seen, and in only one was auricular flutter present. Each received digitalis, and it might be thought that this was the cause of the block. In both instances, however, after complete block had supervened, digitalis was discontinued for considerable periods of time; nevertheless, the block persisted. Thus it seems more probable that the cause was progressive organic damage due to coronary artery disease. Indeed, in the second case, at post mortem, an area of fibrosis in the region of the main branch of the bundle of His was found. In the cases previously reported, quinidine sulfate stopped the flutter in five instances out of twenty-five, digitalis in two, and thyroideectomy in the only case of thyreotoxic heart disease. In the present series both patients received digitalis and one quinidine, but the abnormal rhythm persisted. The prognosis in the presence of the associated conditions is grave; one of our patients lived for six months and the other for seventeen months after the combination of rhythm disorders appeared. Signs and symptoms of right- and left-sided heart failure were present in each instance. The condition can be suspected clinically by observing the occurrence of rapid auricular pulsations in the jugular veins in a patient with a regular ventricular rate between 30 and 40. The diagnosis, however, can be made with certainty only by means of the electrocardiogram.

SUMMARY

Two cases of auricular flutter with complete heart block are reported. In both, the cause appeared to be coronary artery disease, and in neither were the abnormal rhythms affected by therapy.

REFERENCES

1. Jolly, N. A., and Ritchie, W. T.: Auricular Flutter and Fibrillation, *Heart* 2: 177, 1910-11.
2. Jourdonais, L. F., and Mosenthal, H. O.: Complete Auriculoventricular Block and Auricular Flutter with Observations of the Effect of Quinidine Sulfate, *AM. HEART J.* 14: 735, 1937.
3. Willis, F. A.: Auricular Flutter with Established Complete Heart Block, *AM. HEART J.* 2: 449, 1927.

Department of Reviews and Abstracts

Selected Abstracts

Cossio, Pedro: Acoustic Phenomena of the Mitral Valves. Rev. argent. de cardiología. 4: 383, 1938.

The graphic registration of the heart sounds, together with other manifestations of the heart action in 40 cases of mitral stenosis (with and without auricular fibrillation), has shown that very often extra sounds occur in these cases early in diastole: opening snap of the mitral valve, reduplications of the second sound, or an especial sound towards the end of the rapid ventricular inflow. They explain the three and even four sounds often heard in mitral stenosis.

The opening snap occurs more frequently in older patients with predominant signs of stenosis. The rapid ventricular inflow sound occurs more likely in children and adolescents with recent rheumatic aggression and with predominant insufficiency of the mitral valve. The latter may be an ordinary third heart sound with a new acoustic element added, the result of the sudden tension of the diseased valve, caused by the distention of the ventricular wall. Sometimes it may be entirely due to this valvular tension, justifying the name of "tension snap" of the mitral valve.

The phonocardiograms nearly always show a diastolic murmur due to the stenosis and a systolic murmur due to the insufficiency of the valve. Sometimes only one of them is heard, and one gets the wrong impression that only one condition exists. The diastolic murmur begins a short interval after the second sound and shows two reinforcements: protodiastolic and presystolic. Both are fused together when the rapid ventricular inflow and the auricular systole fall together on account of tachycardia. Occasionally the diastolic murmur begins a short interval after the opening of the auriculoventricular valves, and this is interpreted on the assumption that the stenosis is not very great; consequently the conditions to produce the murmur arise only when the ventricular cavity reaches a certain volume. The presystolic murmur may be absent after long diastoles because of the inability of the auricle to inject blood in an overdistended ventricle.

The systolic murmur has variable characteristics and duration. It may be proto- meso- or holo-systolic according to the extent of the lesion or to the moment of its evolution. The following scheme may be drawn for the acoustic phenomena in cases of rheumatic disease of the mitral valve:

a. If the stenosis is slight and recent there is a proto- and meso-systolic murmur which predominates over the diastolic one, the latter even being inaudible; in the records the diastolic murmur may begin after the sound occurring during the rapid ventricular inflow.

b. If the stenosis is frank and older, there is a holo-systolic murmur, and the diastolic one starts either with the ventricular inflow, after the opening snap, or towards the end of that period, following the third sound above mentioned.

c. If the stenosis is marked and very old, there is a proto-systolic murmur masked by the first heart sound, and the diastolic murmur begins after the opening snap, nearly always present.

AUTHOR.

Heymans, Corneille: Experimental Arterial Hypertension. *New Eng. J. Med.* 219: 154, 1938.

The methods of producing hypertension experimentally are reviewed. The four methods described are as follows:

1. Section of the cardio-aortic and carotid sinus moderator nerves. Hypertension occurs here by the release of vasoconstrictor and cardioaccelerator centers, the activity of which, under normal conditions, is permanently moderated reflexly by the cardio-aortic and carotid sinus nerves.

2. Injection of a kaolin suspension into the cerebral ventricles or into the sub-arachnoid space. The mechanical compression thus produced leads to cerebral anoxemia, which particularly sensitizes the vasopressor centers to the stimulating action of carbon dioxide.

3. The production of renal ischemia through permanent, incomplete compression of the renal artery. It is suggested that the arterial hypertension induced by renal ischemia may be due to a humoral factor which increases the excitability of the peripheral blood vessels to constrictor stimulations, mainly to the neurogenic vasoconstrictor influences. The same humoral factor induces, on the other hand, a direct peripheral vasoconstriction and a disturbance in the physiologic mechanisms of the pressoreceptive reflex regulation of blood pressure.

4. Repeated large doses of vitamin D₂ (Calciferol) in dogs produces a progressive augmentation of the arterial blood pressure with the development in the kidneys, and elsewhere, of certain vascular lesions, mainly "arteriolonecrosis."

NAIDE.

Wilson, C., and Pickering, G. W.: Acute Arterial Lesions in Rabbits With Experimental Renal Hypertension. *Clin. Sc.* 3: 343, 1938.

Acute arterial lesions structurally identical with those of malignant hypertension in man have been found in rabbits with arterial hypertension produced by renal artery constriction. The incidence of the lesions was related to the degree of hypertension but not to its duration. These lesions were most frequent and severe in the intestine, but were also found in stomach, liver, suprarenal, heart, and eye; they were absent from the kidney, the renal artery to which had been constricted. It is suggested that a greatly raised intra-arterial pressure is a chief factor in determining these lesions in human and experimental hypertension.

HINES.

Moore, L. A., Hallman, E. T., and Sholl, L. B.: Cardiovascular and Other Lesions in Calves Fed Diets Low in Magnesium. *Arch. Path.* 26: 820, 1938.

Calves fed rations low in magnesium to the extent that the blood magnesium was reduced to a low level exhibited a definite pathologic picture. The principal pathologic alteration consisted of a deposition of calcium salts in the yellow elastic fibers of the endocardium, of the aorta, jugular vein and larger arteries, of the surfaces of the diaphragm and of the trabeculae and capsule of the spleen. Also notable were degeneration and calcification of Purkinje fibers. There were present also various degrees of hepatitis and nephritis. A possible relationship of diets low in magnesium to the arteriosclerosis of human beings is suggested.

AUTHORS.

Roth, Grace M., Maclay, Elizabeth V., and Allen, Edgar V.: Blood in Thromboangiitis Obliterans. *Arch. Int. Med.* 62: 413, 1938.

The values for serum calcium, serum protein, blood urea, serum lecithin and serum phosphorus were found to be within normal limits in a study of the blood in cases of thromboangiitis obliterans. In most instances the blood volume, hematocrit value and concentration of fatty acids and cholesterol in the plasma were found to be normal. In some instances the blood volume was slightly decreased, and the hematocrit value and the concentration of fatty acids and cholesterol in the plasma were slightly increased. The significance of these findings is doubted, since they are inconstant findings in thromboangiitis obliterans.

AUTHORS.

Stanojevie, L.: Determination of Circulation Time With Lobelin. *Ztschr. f. Kreislaufforsch.* 30: 521, 1938.

By using intravenous Lobelin (0.03 to 0.07 mg./kv.) the author determined circulation time objectively, since this drug produced coughing. The determination is simple and without risk. It can be repeated safely several times a day or after a few hours without signs of intolerance cumulation or toxicity. If desired, this can be recorded graphically with a pneumograph. It operates apparently on the cough center since the circulation time is of the order obtained with other methods, viz., on the average 10.6 seconds in normal subjects, 12.8 seconds in noncardiac patients, 13.4 seconds in cardiac patients without congestive failure and 30.2 seconds in congestive failure.

KATZ.

Korth, C.: Frontiers of Clinical Electrocardiography. *Arch. f. Kreislaufforsch.* 3: 1, 1938.

The recent advances in clinical interpretation of the electrocardiogram are evaluated in view of recent work. It was found that inverted T-waves are more significant when in Leads I or I and II than when in Lead III. Abrupt changes in direction of T are particularly significant. In infectious diseases, the T-wave contour is important in estimating myocardial damage. The S-T segment has gained greater meaning clinically within recent years. The value of electrical systole in tetany is stressed. Considerable value is to be attached also to the axis deviation.

KATZ.

Rühl, A.: The Significance of Severe Anoxic Variations of the T Wave in Healthy Subjects. *Ztschr. f. Kreislaufforsch.* 30: 393, 1938.

The electrocardiographic variations were noted on placing normal subjects in a low pressure chamber and lowering the atmospheric pressure to the equivalent of altitudes of from 16,250 to 21,125 feet. A total of 118 observations were made. It was found that T was flattened in Leads I and II and S-T was depressed in these leads. Exercise before subjecting the individual to the high altitudes increased the deviation of S-T and T.

KATZ.

Schlomka, G., and Dietrich, H.: Physiological Arrhythmia of the Heart. VI. In Emphysema. *Ztschr. f. Kreislaufforsch.* 30: 453, 1938.

One hundred patients were studied. The results are opposed to the view that the sinus arrhythmia is not caused by a central radiation of impulses from the

respiratory to the cardioregulatory centers. The sinus arrhythmia increases in degree at first as the lung involvement increases and then with further lung involvement tends to decrease.

KATZ.

Walter, R.: Correlation Between Pulse Frequency and Conduction Time as a Sign of Myocarditis. *Ztschr. f. Kreislaufforsch.* 30: 481, 1938.

A prolonged P-R interval is an early sign in myocardial inflammation. This is accompanied by tachycardia. Tachycardias such as follow exertion in normal individuals differ from the tachycardias in damage to the heart muscle in that the former are unaccompanied by prolongation of P-R. However, even in myocarditis, tachycardia following exertion is not associated with prolongation of P-R.

KATZ.

Schlomka, G., and von Königslöw, E.: The Evaluation of the Relative Duration of Systole. IV. Extrasystoles. *Ztschr. f. Kreislaufforsch.* 30: 487, 1938.

When correlated with the duration of the preceding diastole, the systole of the postextrasystolic beat following a compensatory pause was found to be relatively longer than the other sinus beats. This was less noticeable following supraventricular extrasystoles than following ventricular ones. This relative prolongation of systole is also less marked in diseased hearts than in normal ones.

KATZ.

Langendorf, R., and Pick, A.: Electrocardiogram in Acute Nephritis (two parts). *Acta Med. Scandinav.* 94: 1, 1938.

This is a report on twelve cases of acute diffuse glomerular nephritis. A flattening or inversion of T was found in Lead I, with a bifid T-wave in some cases, and in Lead III (and II) T became large and upright. In Lead IV, T became inverted (new terminology) and sometimes T became bifid. The absence of S-T deviations and Q-wave changes distinguish this condition from coronary occlusion with myocardial infarction. The discordancy of changes in Leads I and III and the absence of S-T changes distinguish this type from that in pericarditis.

In the evolution of the changes, the T-wave in Lead I becomes inverted and T₂ becomes typically peaked, and Lead IV develops a deep T, resembling superficially the changes in anterior myocardial infarction. The author attributes changes to heart strain on the left side which is caused by the sudden hypertension, but this is not the sole cause as some ischemic, toxic, or other effects on the myocardium must play a rôle.

KATZ.

Winternitz, M., and Langendorf, R.: The Electrocardiogram in Pericarditis. *Acta Med. Scandinav.* 94: 141, 274, 1938.

This is a report of 76 cases of pericarditis including 8 of traumatic origin with hemopericardium, 18 of rheumatic origin, 14 of tuberculous origin, 12 of uremic origin, 2 due to blastomastosis, 11 of a septic nature, 5 following myocardial infarction, and 5 of unknown origin. These cases are critically reviewed and correlated with the literature on the subject. Characteristic changes occurred in 46 cases, no change in 15, and noncharacteristic abnormalities in the rest. Most characteristic early in the disease is the presence of an elevated S-T segment concave upward followed by an upright T-wave. The terminal portion of QRS is pulled upward. These early changes last for about three days, when S-T deviations disappear and T

becomes flatter. Later T becomes inverted, but the T-wave and S-T evolution are not coordinated in time. Also, before becoming inverted, T may be split, or appear as a late, small deflection. Later T becomes a characteristic coronary type and waxes and wanes. Precordial leads are not characteristic of the lesion but fail to show the typical coronary occlusion evolution. The cause for electrocardiographic changes is not due to ischemia of muscle or tamponade or to subepicardial myocardial damage, but the authors consider them due to bioelectric changes in the tissues surrounding the heart. The negative T-wave, however, is due to an action in the heart.

KATZ.

Master, Arthur M., Dack, Simon, and Jaffe, Harry L.: **Partial and Complete Heart Block in Acute Coronary Artery Occlusion.** *Am. J. M. Sc.* 196: 513, 1938.

A complete review has been made of the A-V conduction disturbances in 375 cases of coronary artery occlusion with reference to their incidence, clinical, electrocardiographic and pathologic features, prognosis and treatment.

Simple P-R prolongation was common, occurring in 16 per cent of cases; partial and complete heart block occurred in 3.2 per cent.

Heart block appeared soon after the onset of the occlusion and usually lasted one to two weeks. P-R prolongation not infrequently appeared late and became permanent.

Permanent P-R prolongation and heart block may be the result of previous unrecognized coronary occlusion. Repeated attacks of occlusion may progressively increase the A-V conduction defect.

The sudden onset of P-R prolongation as well as heart block may be the first and only sign of coronary artery occlusion.

Heart block, excluding P-R prolongation, was associated with heart failure, cardiac enlargement, previous hypertension, and previous coronary occlusion. It was more common in older patients with advanced arteriosclerosis.

Symptoms attributable to the heart block appeared only when the ventricular rate fell to 40 or less and consisted of heart failure or the Stokes-Adams syndrome with syncope and coma. The bradycardia can differentiate the latter from syncope and coma due to other causes, such as shock and cerebral embolus.

The prognosis of complete heart block was serious, because of the slow ventricular rate. Four of the six patients died. Partial heart block offered a favorable prognosis unless there was marked bradycardia. Simple P-R prolongation did not affect the outcome of an attack adversely.

It was confirmed that complete and partial heart block were associated with a specific cardiac lesion and electrocardiographic pattern. The anatomic basis was infarction of the posterior portion of the interventricular septum and posterior surface of the left ventricle as a result of right coronary artery occlusion. The electrocardiogram presented the Q-3 T-3 pattern typical of posterior wall infarction.

The presence of profuse anastomotic channels in the interventricular septum around the A-V node prevents the more frequent occurrence of heart block and affects its remission when it does occur.

P-R prolongation was not associated with a specific anatomic lesion or electrocardiographic pattern. Anoxemia, heart failure, and vagal influences were probably significant.

The association of A-V block with intraventricular block can be attributed to septal infarction which involves simultaneously the A-V tissues and bundle-branch system.

The treatment of heart block is that of coronary artery occlusion in general. When there are persistent bradycardia and Stokes-Adams manifestations, adrenalin

should be resorted to. The indications and effects of adrenalin, ephedrine, and atropine are discussed. Digitalis, quinidine, and nitroglycerine were considered contraindicated.

AUTHOR.

Hadorn, W.: Combined Thrombo-Emboli of the Coronary Arteries. *Ztschr. f. Kreislaufforsch.* 30: 563, 1938.

An unusual case is reported where a thrombus over a myocardial infarction gave rise to an embolus which lodged in the same coronary artery in which an earlier thrombus had resulted in the infarction. This coronary embolus caused sudden death of the patient.

KATZ.

Hines, E. A., Jr., and Roth, Grace M.: The Effect of Tobacco on the Blood Pressure as Measured by a Standard Smoking Test. *Proc. Staff Meet., Mayo Clin.* 13: 524, 1938.

A standard smoking test and a control test have been carried out on fifty-six patients with essential hypertension and thirty subjects with normal blood pressure. Cigarette smoke produced an elevation of blood pressure in the majority of individuals tested by a standard smoking test. The excessive rises in blood pressure from smoking occurred only in the patients who had evidence of an inherently hyperreactive vascular system as measured by the cold pressor test. The effect of smoking tobacco on the blood pressure, however, is not due entirely to a nonspecific stimulus acting on a hyperreactive vascular system but is the result, at least in part, of some element in the tobacco smoke which produces vasoconstriction.

AUTHORS.

Alam, M., and Smirk, F. H.: Blood Pressure Raising Reflexes in Health, Essential Hypertension, and Renal Hypertension. *Clin. Sc.* 3: 259, 1938.

A study has been made of the effects of blood pressure raising reflexes in normal subjects, patients with essential hypertension, and patients with renal hypertension. Two different methods of testing the blood pressure raising reflexes were employed: (1) the stimulus of exercising the forearm muscles during arrest of the circulation as previously described by the authors; (2) a modification of the cold pressor test as described by Hines and Brown. Effects on the blood pressure were similar with both tests. It was found that the effects on the systolic blood pressure are greater in old than in young subjects but there was no difference in the effect of age on the diastolic pressure. The rise in both systolic and diastolic pressures is less in patients with renal hypertension than in normal subjects of the same age group. Large effects are more frequent in cases of essential hypertension than in normal controls of the same age. Large rises of blood pressure may occur in normal subjects and small rises in patients with essential hypertension. No definite correlation was found between a high degree of reactivity and the resting blood pressure level. In the majority of cases of essential hypertension the natural relationship between the pulse rate and blood pressure is reversed in that a rise in blood pressure is accompanied by a rise in pulse rate.

HINES.

Barker, Nelson W.: Lesions of Peripheral Nerves in Thromboangiitis Obliterans. *Arch. Int. Med.* 62: 271, 1938.

In a histopathologic study of the peripheral nerves in a series of twenty cases of thromboangiitis obliterans various combinations of wallerian degeneration, fibrosis,

edema, atrophy, lymphocytic infiltration, inflammation and thrombosis of the vasa vasorum were noted in all but one case. A definite correlation was found between the presence of wallerian degeneration and the clinical syndrome of ischemic neuritis. The presence of these degenerative changes proximal to the site of nerve section or alcohol injection explains the failure to relieve pain with these procedures.

NAIDE.

Saleeby, Eli R., and McCarthy, Patrick A.: Aneurysms. *Pennsylvania M. J.* 41: 969, 1938.

Thoracic and abdominal aneurysms can be prevented by early and intelligent treatment of syphilis.

The Matas obliterative endoaneurysmorrhaphy offers the best available means of cure for external aneurysms.

The present treatment of internal aneurysms is unsatisfactory.

The Babcock procedure of end-to-end anastomosis of the common carotid artery and internal jugular vein offers the best available means of alleviating the symptoms of intrathoracic and subclavian aneurysms untreatable by other means.

There have been no instances of rupture of an intrathoracic aneurysm following the Babcock procedure.

AUTHOR.

Cleland, J. B.: Periarthritis Nodosa; Report of Two New Cases. *M. J. Australia* 1: 847, 1938.

There seems to be a definite relationship between periarthritis nodosa and rheumatic fever, and it is possible that the former disease is in some cases an allergic response to the agent of rheumatic fever. Three cases of periarthritis nodosa were found in 4,000 autopsy cases in two Australian hospitals. One of these three cases presented rheumatic vegetations on the mitral valve. Allusion is made to previous cases with associated rheumatic manifestations. The cause of periarthritis nodosa, of course, has not been proved.

MONTGOMERY.

Fatherree, T. J., and Hines, E. A., Jr.: Fatal Complications of Thrombo-Angiitis Obliterans: A Clinical Study. *Proc. Staff Meet., Mayo Clin.* 13: 342, 1938.

The cases are reported of twenty-two individuals with thromboangiitis obliterans who died, including nine on whom necropsy was performed. In sixteen cases, or 73 per cent of the group, extraperipheral vascular lesions played a dominant role as the cause of death. Four of these deaths followed operation. Coronary thrombosis is by far the most common type of peripheral lesion producing death in cases of thromboangiitis obliterans. In none of the post-mortem cases was a lesion found in the visceral arteries which was typical of the pathologic changes described by Buerger.

AUTHORS.

Lewis, Thomas: Raynaud's Disease and Preganglionic Sympathectomy. *Clin. Sc.* 3: 321, 1938.

Six unselected cases of Raynaud's disease have been examined shortly after preganglionic sympathectomy. Observation of these cases shows that preganglionic sympathectomy does not bring the fingers to a common state; it relieves in all cases, but a local abnormality remains, and this can be displayed in a measure that is re-

lated to the abnormality displayed before operation. The full vasodilatation resulting from preganglionic sympathectomy declines in a period of about a week following operation.

HINES.

Rosenberg, Edward F., Keith, Norman M., and Wagener, Henry P.: Diffuse Arterial Disease With Hypertension: Two Unusual Cases of Contrasting Types. *Arch. Int. Med.* 62: 461, 1938.

The term diffuse arterial disease when used in a broad sense includes cases in which there are primary changes both in the arteries and in the arterioles. Two contrasting cases are reported in which the preponderant alteration in one was in the arterioles, whereas in the other it was in the arteries.

In the first case, with arteriolar involvement, the retinal picture was characterized by diffuse edema of the retina and of the optic nerve, with various hemorrhagic and exudative lesions and with visible changes in the retinal blood vessels. In the second case, with sclerosis of the larger arteries, the retinal changes were minimal, consisting of mild arteriovenous compression and mild narrowing of the retinal arterioles; a slight change in the color of the arterioles was also present.

The general conclusion is drawn that in patients with sustained hypertension, the site of the predominating change, whether it is an abnormal physiologic process or an actual anatomic lesion, is in the arterioles; on the other hand, in patients with diffuse atherosclerosis of the arteries, hypertension is often mild and fluctuating or even absent.

NAIDE.

Clara, M.: Anatomy and Biology of the Blood Supply of the Kidney. *Arch. f. Kreislaufforsch.* 3: 42, 1938.

An excellent summary beautifully illustrated is presented of the architecture of the renal vascular supply based on the author's work correlated with that in the literature.

KATZ.

Bähr, E.: Atherosclerosis of the Coronary Arteries in Relation to Age, Disease and Constitution. *Arch. f. Kreislaufforsch.* 3: 95, 1938.

A study based on 308 autopsies of subjects from 4 months to 92 years of age is presented in which analysis of macroscopic changes in the major coronary vessels was made. A novel type of diagram was used to depict the distribution of atherosclerosis in the coronaries at various age groups. It was found that the left descending coronary is the one involved earliest and the one which is most intensely involved at all age groups. The left circumflex is least involved and the right circumflex is intermediary. Exceptions to this occur when the right coronary artery is unusually long or the right ventricle is hypertrophied. Atherosclerosis increases with increased work of the heart. The so-called white collar class and professional groups show more involvement of the coronaries than manual laborers. The florid and robust type of person has coronary sclerosis while the asthenic has this disease only on rare occasions.

KATZ.

Anthony, A. J., and Lent, W.: The Distensibility of the Vessels of the Extremities. III. *Ztschr. f. Kreislaufforsch.* 30: 528, 1938.

Curves of distensibility of the arteries of the extremities were obtained by correlating the pulse wave velocity with the "wirksam" internal pressure. Marked individual variations were obtained in young, healthy persons while the curves of old

persons were similar in shape. Little differences were seen in the average curve obtained from healthy young people, old people, and hypertensive patients. On the whole, the distensibility of the healthy subjects was greater at low pressures.

KATZ.

Grant, R. T., and Holling, H. E.: Further Observations on the Vascular Responses of the Human Limb to Body Warming; Evidence for Sympathetic Vasodilator Nerves in the Normal Subject. Clin. Sc. 3: 273, 1938.

Recent observations have revealed that while body warming provokes a large increase of blood flow and skin temperature in the hands and feet it causes no more than a slight rise in blood flow and skin temperature in the proximal part of the extremities, and neither flushing nor warming of the skin of the proximal portion occurs provided the circulation to the extremity is arrested. This variation has been explained as being due to the difference in the distribution of the arteriovenous anastomoses. The present study was carried out to see if further information could be obtained as to the reason for the difference in reactions. The subjects to be tested were subjected to strong body warming accomplished by immersing two or three extremities in water maintained at 45 to 46° C. and with other portions of the body completely covered except the face and the limb under observation. Blood flow and skin temperature were measured by methods previously described. It was found that when body warming was pushed to excess in this manner vasodilation develops in the proximal areas of the extremities. Observations were made in several patients before and after sympathetic ganglionectomy and on several subjects following nerve block. The results obtained from these and previous observations are interpreted as indicating two means of defense against rise in body temperature. The first is brought into action by relatively gentle heating and consists chiefly of a dilatation of the arteriovenous anastomoses in the extremities caused by the inhibition of vasoconstrictor tone. The second occurs when the heating is more intense and consists mainly of a general dilatation of the cutaneous vessels associated with sweating. The vasodilation produced in the proximal part of the extremity is brought about by stimulation of cutaneous sympathetic nerves.

HINES.

Stewart, Harold J., Deitrick, John E., Crane, Norman F., and Wheeler, Charles H.: Action of Digitalis in Uncompensated Heart Disease. Arch. Int. Med. 62: 561, 1938.

From the detailed study of the mechanism of the action of digitalis on the circulation of forty-two patients suffering from heart disease the following conclusions are drawn:

The output of blood per minute from the heart which is in failure is diminished, the velocity of the blood flow is less and the heart is larger than when it is in a state of compensation. The work per beat is decreased and is not commensurate with the size of the organ. The venous pressure is in certain instances elevated, and in others it is in the normal range.

Digitalis increases the output per minute of the failing heart, decreases its size and increases the work per beat, so that it more nearly approximates what is expected of it for its size. The circulating blood now moves at a greater velocity. A fall in venous pressure occurs if it was elevated beforehand.

An interpretation of these results in the light of those already reported is that digitalis has the same action on the normal as on the pathologic heart; it decreases the cardiac size, which is interpreted as an effect on tone. The amount of the cardiac output which results from this action depends on the initial size of the heart.

The amount decreases in the case of a normal heart and increases in the case of a dilated one. The evidence indicates that digitalis acts in a similar fashion on the normal heart and on those damaged by valvular disease and by myocardial disease unless the myocardial damage is extreme, in which case toxic effects might possibly be elicited at lower concentrations of digitalis.

The effect of digitalis in the presence of auricular fibrillation is similar to that recorded when the rhythm is regular.

The response of hearts damaged by syphilis, arteriosclerosis, and hypertension appears to be similar to that observed for hearts damaged by rheumatic fever.

The response of patients whose aortic valves are damaged is not different from that of patients exhibiting mitral involvement.

The decrease in cardiac size appears to be the most important effect of digitalis, the change in cardiac output being a consequence of it.

The lowering of the venous pressure by the administration of digitalis to the patient exhibiting heart failure seems to be dependent on an increase in cardiac output. An increase in cardiac output and work per beat permits the pumping onward of the blood accumulated on the right side so that a proper distribution results.

There are indications that digitalis may benefit certain patients with organic heart disease without heart failure (Christian), but the final proof will depend on clinical observations.

When considered in the light of data relating to the action of the drug when the heart is normal and to its action when the heart is damaged by organic heart disease but heart failure is not present, the observations now reported with respect to patients with failure, those presenting regular sinus rhythm as well as those exhibiting auricular fibrillation, lead the authors to restate their original conclusion. Digitalis has similar, perhaps identical, action when the heart is normal and when it is diseased. It decreases the cardiac size and increases the extent of ventricular contraction, and to these is to be added the effect on systolic tension. The consequence of these actions is that the cardiac output which results differs, depending on the initial difference in the size of the ventricular cavities in the two situations. In the one (the normal heart and the diseased heart which is not failing) it becomes too small; in the other (the diseased heart which is failing) it acquires a suitable size.

These studies demonstrate, however, a more uniform generalization which is applicable to all these situations, namely, that digitalis increases the work of the heart per beat and that with respect to the heart which is failing, it increases the work per beat and makes it more nearly commensurate with the work expected of the heart for its size.

AUTHORS.

Stewart, Harold J., Crane, Norman F., Deitrick, John E., and Thompson, W. P.: Action of Digitalis in Compensated Heart Disease. *Arch. Int. Med.* 62: 547, 1938.

The authors gave 1.6 to 1.8 gm. of digitalis within twenty-four hours to thirteen patients suffering from rheumatic heart disease and to four others with arteriosclerotic, hypertensive or syphilitic heart disease. In all cases there was compensation, and a normal sinus mechanism was exhibited. In addition to clinical studies of these patients, special observations were made of the cardiac output, cardiac size, circulation time, and venous pressure. In all cases the T-wave and the R-T segment of the electrocardiogram showed the changes characteristic of a digitalis effect. It was found that seven patients showed a decrease in cardiac output and a decrease in cardiac size, four patients showed an increase in cardiac output and a decrease in cardiac size, and six patients showed no change in cardiac output and in cardiac

size. In short, in some instances when the heart was made smaller, the cardiac output increased, and in others it decreased. In the former cases the heart behaved like a failing heart, and in the latter cases like a normal one. They were unable to predict beforehand which effect would be produced.

The results in five patients exhibiting auricular fibrillation were not different from those encountered in those with normal sinus rhythm—a decrease in cardiac size was associated with a decrease in cardiac output, and an unchanged cardiac size was associated with an unchanged cardiac output.

Digitalis has four effects on the heart which may be recorded clinically: (1) an effect on contraction, namely, an increase; (2) an effect on size, namely, a decrease; (3) an effect on the cardiac rate, namely, a decrease; and (4) an effect on the electrocardiogram, indicating an effect on the cardiac muscle. The cardiac output which results is different, depending on the individual heart, that is to say, whether it is dilated or not.

A few observations on patients with heart disease due to other etiological factors showed that these phenomena are not confined to those with rheumatic involvement.

There is one phenomenon which is common to all groups: The giving of digitalis increases the work accomplished by the heart per beat, whether its action is to increase or to decrease the output or to leave it unaltered and whether the rhythm is regular or is that of auricular fibrillation. As a consequence, work becomes more nearly appropriate for the size of the organ. Some basis is afforded Christian's suggestion of giving digitalis to the patient suffering from organic heart disease even though he shows no significant failure.

These studies yield additional evidence that a decrease in cardiac output which follows the giving of digitalis to human beings (normal and those having organic heart disease without congestive heart failure) is not a consequence of diminished venous return but a consequence, so far as we can now ascertain, of a decrease in the size of the heart due to the action of digitalis on it.

AUTHORS.

Von Storch, Theodore J. C.: Complications Following the Use of Ergotamine Tartrate. J. A. M. A. 111: 293, 1938.

Analysis of all the reports of serious sequelae following the use of ergotamine tartrate reveals that the great majority of the complications arose because of overdosage, pre-existing sepsis, or obliterative vascular disease. Twenty-one of the total of forty-two patients reported in the literature developed gangrene. No accidents have been reported following its use in the migraine syndrome.

Treatment, by the author, of 189 patients with migraine headaches over a period of five years has resulted in no serious complications.

Contraindications to the use of ergotamine tartrate are sepsis and obliterative vascular disease, including disease of the coronary arteries. Caution should be used in the presence of marked arteriosclerosis, hepatic or renal disease, vitamin C deficiency, and hypersensitivity to the drug.

When correctly administered and attention is paid to warning symptoms ergotamine tartrate may be considered a safe and valuable method for the treatment of migraine headaches.

NAIDE.

American Heart Association, Inc.

RADIO CITY

50 WEST 50TH STREET, NEW YORK, N. Y.

DR. WILLIAM J. KERR
President

DR. WILLIAM D. STROUD
Vice-President

DR. HOWARD B. SPRAGUE
Secretary

DR. WALTER W. HAMBURGER
Treasurer

BOARD OF DIRECTORS

DR. T. HOMER COFFEN Portland, Ore.
DR. CLARENCE DE LA CHAPELLE

New York City

DR. WALTER W. HAMBURGER Chicago

DR. GEORGE R. HERRMANN Galveston

DR. EMMET F. HORINE Louisville

*DR. WILLIAM J. KERR San Francisco

*DR. EMANUEL LIBMAN New York City

DR. HUGH MCCULLOCH St. Louis

*DR. GILBERT MARQUARDT Chicago

*DR. H. M. MARVIN New Haven

*DR. EDWIN P. MAYNARD, JR. Brooklyn

DR. JONATHAN MEAKINS Montreal

*DR. FRANKLIN NUZUM Santa Barbara

DR. STEWART R. ROBERTS Atlanta

DR. WILLIAM H. ROBEX Boston

DR. ROY W. SCOTT Cleveland

*DR. HOWARD B. SPRAGUE Boston

*DR. WILLIAM D. STROUD Philadelphia

DR. LOUIS VIKO Salt Lake City

DR. HOWARD F. WEST Los Angeles

DR. PAUL D. WHITE Boston

DR. FRANK N. WILSON Ann Arbor

DR. CHARLES C. WOLFERTH Philadelphia

*DR. IRVING S. WRIGHT New York City

*DR. WALLACE M. YATER Washington, D. C.

DR. H. M. MARVIN, *Acting Executive Secretary*

GERTRUDE P. WOOD, *Office Secretary*

TELEPHONE CIRCLE 5-8000

THE American Heart Association, sponsor of the first International Health Broadcast, stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is \$5.00 a year and journal membership at \$10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

**Executive Committee.*

The American Heart Journal

VOL. 17

FEBRUARY, 1939

No. 2

Original Communications

REVERSIBLE CARDIAC ENLARGEMENT IN A CASE OF CONGENITAL CAVERNOUS HEMANGIOMA

RUDOLPH MATAS, M.D., AND B. R. HENINGER, M.D.
NEW ORLEANS, LA.

THE clinical entity known as the "reversible heart" has attracted the attention of both physiologists and clinicians for many years, although the term now used to identify it came into use only very recently. As early as 1847, Boisscau, as Matas points out,¹ described such a condition in association with arteriovenous fistula. In 1918, Zondek² emphasized the fact that in both myxedema and beriberi the heart might dilate and might even fail as the result of specific deficiencies, and observed that in cases of myxedema the administration of thyroid extract was followed by a return to normal cardiac dimensions. In 1925, Fahr³ confirmed Zondek's observations on myxedema and reported a case in which a decrease of more than 6 cm. was noted in the transverse cardiac diameter after thyroid therapy. He also demonstrated that withdrawal of the thyroid extract, after the heart had returned to its normal dimensions, was followed by redilatation, and sometimes by cardiac failure.

Zondek's findings were further confirmed by Davis,⁴ by Hallock⁵ and by Gordon,⁶ and various explanations for them were adduced. Thus, Hallock expressed the view that the cardiac enlargement associated with myxedema is the result of a hypodynamic state of the myocardium, which necessitates a compensatory dilatation for the maintenance of normal minute volume. Gordon considered that the rapid decrease in the size of the cardiac shadow after the use of thyroid extract may be due to reabsorption of the pericardial fluid.

A similar decrease in the size of the heart follows the administration of vitamin B in cases of cardiac enlargement caused by beriberi. A deficiency in vitamin B, according to Wennekebach,⁷ induces physiochemical changes which cause water retention and intercellular edema.

From the Department of Surgery, Tulane University School of Medicine, and the Department of Medicine, Louisiana State University School of Medicine, New Orleans, La.

Received for publication August 1, 1938.

The microscopic changes which he demonstrated were confirmed by Weiss and Wilkins,⁸ who did not, however, consider them to be of a specific character, and they were also confirmed by Keefer⁹ and by Kepler.¹⁰ All of these observers also reported the relief of cardiac symptoms and the return of the heart to normal size after the administration of vitamin B.

In 1923, Matas, in a report of 31 cases of arteriovenous aneurysm, described at considerable length the effect of this abnormality upon the size of the heart. At this time there was no unanimity of opinion upon this point. Lewis and Drury¹¹ believed that the cardiac enlargement resulting from arteriovenous fistula was essentially a dilatation. Holman,¹² on the other hand, proved experimentally that there was definite hypertrophy as well as dilatation; the weight of the hearts of his experimental animals was found to be increased post mortem. His idea was that the cardiac hypertrophy was due to the "increased work necessary to propel forward this increasing volume of blood flowing through" the heart. Eyster,¹³⁻¹⁶ some years later, carried the explanation still further by postulating the injury theory, his idea being that injury to the heart muscle as the result of dilatation may be the reason for the ultimate hypertrophy.



Fig. 1.

Fig. 2.

Fig. 1.—R. B. Teleoroentgenogram of heart and aorta, iliofemoral arteriovenous fistula open, before compression. Longitudinal diameter of heart, 16.3 cm.; transverse diameter, 15 cm. (Matas).

Fig. 2.—R. B. Teleoroentgenogram of heart and aorta, fifty-two days after surgical suppression of the fistula. Longitudinal diameter of heart 14.8 cm.; transverse diameter, 13.3 cm. (Matas).

In 1936, Walker¹⁷ discussed the "reversible heart" under three headings: arteriovenous aneurysm, beriberi, and myxedema. His chief contribution was to emphasize the fact that the hypertrophy is not always permanently irreversible, as was then rather generally supposed, but is frequently, if not usually, curable.

Also in 1936, Rosenblatt¹⁸ discussed cardiac enlargement associated with chronic pulmonary tuberculosis. The enlargement may be very marked, but the institution of intensive diuretic therapy frequently results in a return to normal cardiac dimensions.

Some of the cases of arteriovenous aneurysm described by Matas in 1923 (Figs. 1 and 2) furnished the first opportunity for one of us (B. R. H.) to study the condition now known as "reversible heart." The case reported herewith was one of congenital cavernous hemangioma. Only the cardiovascular aspect is dealt with here; the surgical considerations will be presented elsewhere (R. M.).

CASE REPORT

C. C., a white man, was first seen by us in 1925, at which time he was 21 years of age. We have no very satisfactory account of his early history. At the age of 3 years, after apparently normal development up to that time, the little finger on the right hand had become discolored and later ulcerated. Some years later the same condition seems to have recurred, but no definite diagnosis was made. The patient was next heard of in 1920, at which time he registered at the Mayo Clinic because of an extensive cavernous hemangioma involving the right hand and lower forearm. After a thorough study there, the affected extremity was amputated above the involved area. A year later the condition recurred in the stump and a diagnosis of congenital subclavian arteriovenous fistula was made. Marked cardiac enlargement was reported at the same time.

Early in 1925, during the course of a routine college medical examination, the patient was told that he had an "enormous" heart, a statement which confirmed the previous report from the Mayo Clinic and apparently proved the persistence of the cardiac enlargement over the intervening four-year period. The chief symptoms at this time were dyspnea and easy fatigue.

Both of these symptoms were very marked when the patient was first seen by us in March of the same year. Dyspnea was distressing, and the mere act of undressing for the examination completely exhausted him. Physical examination revealed a tremendous conical enlargement of the stump of the right forearm (Fig. 3) due to the presence of a large, spongy hemangioma; the diameter of the stump was 17.5 cm. A loud systolic murmur was audible over the entire precordium, but was heard best over the mitral and pulmonic areas. A teleoroentgenogram showed that the heart occupied the entire thorax and was enlarged in all diameters (Fig. 4). The blood pressure was 130/80 in the left arm and 102/80 in the right arm, in which it rose to 130/80 when the hemangioma was tightly squeezed. This maneuver was associated with a marked slowing of the pulse rate (Branham's syndrome).

A month after the patient was first seen, Matas ligated the third portion of the right subclavian artery. The local hemangiomatous signs promptly disappeared but returned almost as promptly, and the patient was practically incapacitated by dyspnea. Three weeks after the first operation the right arm was disarticulated at the shoulder joint.

Improvement after the second operation was prompt and marked. Two months later the heart was apparently normal in size, the diameter having been reduced from 17.5 cm. to 13.5 cm. (Fig. 5). The murmur had completely disappeared, and from the clinical standpoint the patient seemed entirely normal.

Nothing more was heard of him until 1933, when it was reported to us by Singer, of St. Louis, that he had contracted a severe toxic pneumonia, accompanied by cardiac collapse, from which he had recovered after a very tedious convalescence. In March, 1936, the patient again consulted Singer because of a recurrence of the hemangioma at the site of the scar and in the right axilla. The heart at this time was normal in size (Fig. 6). A month later Matas removed the entire hemangiomatous mass, and the patient received several x-ray treatments. Radiographic and cardiovascular studies showed that the heart was normal in size (Fig. 7) and adequate in function.



A.

B.

Fig. 3.—A. C. C., aged 19 years. Note recurrence and spread of angioma in stump of forearm (April 1, 1923).

B. C. C., aged 21 years. After ligation of subclavian vessels, with consequent temporary improvement, three weeks later (April 24, 1925) arm was disarticulated at the shoulder.



Fig. 4.—C. C. Plate taken in March, 1925, showing greatly enlarged heart.

In March, 1937, the patient again consulted us because of a recurrence of the hemangioma in the right submammary region. The heart was markedly enlarged; a teleoroentgenogram showed a transverse diameter of 15.8 cm. and a semithoracic diameter of 13.5 cm. (Fig. 8).

At this time the patient was 33 years of age and weighed 149 pounds. The pulse rate when he was at rest was 80, and the blood pressure in the left arm 140/85. The heart sounds were of good quality, there was no arrhythmia, and no murmurs were heard. The aortic second sound was louder than the pulmonic second sound, but neither was accentuated.

Because of the definite cardiac enlargement several tests of function were done. The circulation time (by the decholin method from arm to tongue) was fourteen seconds. The response to the Master two-step test was normal, and the vital capacity was 4.2 liters. Since the heart was apparently capable of efficient function, the patient was discharged after a course of roentgenotherapy. When he was last heard from, in December, 1937, he stated that he had been married for two months, and although he was working harder than he had ever worked before, because of his assumption of new obligations, he "felt better than he had ever felt in his life."

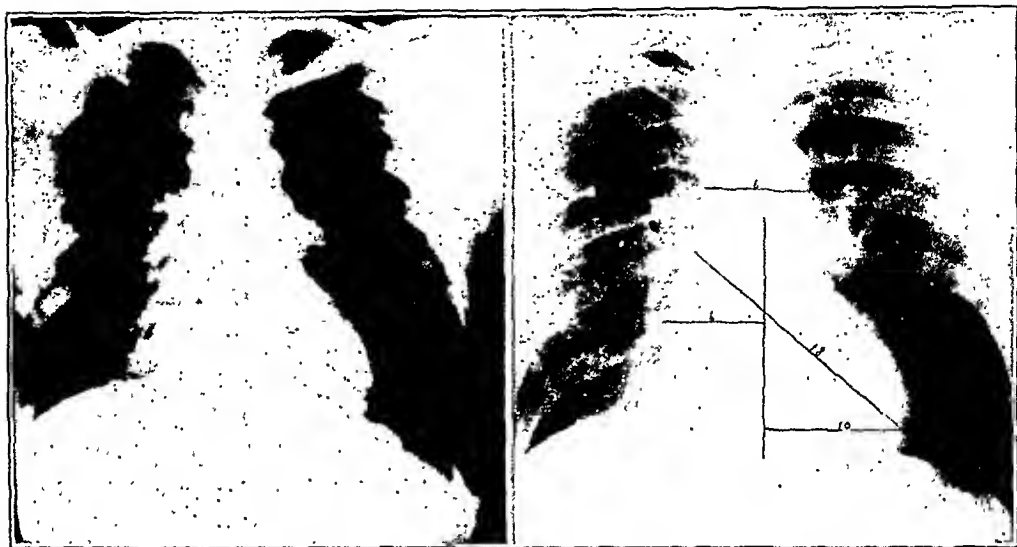


Fig. 5.

Fig. 6.

Fig. 5.—C. C. View showing diminution in size of heart following ligation of subclavian vessels and disarticulation of right arm at the shoulder joint.

Fig. 6.—C. C. Plate taken eleven years after operation shows normal heart, in spite of recurrence of hemangioma at site of scar and in right axilla.



Fig. 7.

Fig. 8.

Fig. 7.—C. C. Radiographic study one month after removal of hemangiomatous mass shows heart normal in size.

Fig. 8.—C. C. View taken in March, 1937, shows a markedly enlarged heart. There has been a recurrence of the hemangioma in right submammary region.

DISCUSSION

It is now generally accepted that no single factor will explain all kinds of cardiac enlargement, especially those in which there is a varying degree of reversibility. It is also believed that the cardiac enlargement which follows vitamin deficiency, for instance, differs from the enlargement associated with arteriovenous aneurysm, even though in both conditions the same basic factors might play some part in the production of the enlargement.

It is our own idea that the mechanism causing the cardiac enlargement in this case is substantially the same as the now thoroughly understood mechanism which produces the increase in the size of the heart in cases of arteriovenous fistula, as postulated by Eyster. We have no specific evidence to confirm or disprove any special theory, but we feel that in our own case there was a true mass hypertrophy of the heart, as well as an initial dilatation. It does not seem plausible that cardiac dilatation without hypertrophy could exist over as long a period of time as it did in this case without the occurrence of heart failure. It is not necessary to commit oneself to a special theory, however, to comprehend what apparently happened in this case. Radiographic evidence showed that a heart which had been dilated and hypertrophied for at least six years returned to approximately normal size and functioned efficiently. Twelve years later the cardiac dilatation and hypertrophy recurred, yet the heart, by standard adequacy tests, was shown to be capable of carrying on its physiologic function in an apparently normal manner.

SUMMARY

1. Congenital hemangioma of the upper extremity has been added to the group of diseases which produce the condition known as "reversible heart."

2. In the case reported, definite cardiac enlargement had persisted for four years prior to amputation of the right arm and forearm for a cavernous hemangioma; after operation the cardiac dimensions returned to normal size. Twelve years later the heart again became enlarged, following a metastasis or activation of hemangiomatous "nests" in the right submammary region. Adequacy tests, however, revealed cardiac competency.

3. The mechanism of the cardiac enlargement in this case is discussed, and the injury theory of Eyster is accepted as the underlying cause of the hypertrophy, just as it is the most reasonable explanation for the reversible cardiac enlargement associated with arteriovenous fistula.

REFERENCES

1. Matas, R.: Systemic or Cardiovascular Effects of Arteriovenous Fistulae, *Tr. South. S. A.* 36: 623, 1923.
2. Zondek. H.: Das Myxoedemherz, *München. med. Wchnschr.* 65: 1180, 1918.
3. Fahr, G.: Myxedema Heart, *J. A. M. A.* 84: 345, 1925.
4. Davis, J. C.: Myxedema Heart, *Ann. Int. Med.* 4: 733, 1931.

5. Hallock, P.: The Heart in Myxedema, *AM. HEART J.* 9: 196, 1933.
6. Gordon, A. H.: Pericardial Effusion, Myxedema, *Tr. A. Am. Physicians* 50: 272, 1935.
7. Wenckebach, K. F.: Heart and Circulation in Tropical Atyraminosis, *Lancet* 2: 265, 1928.
8. Weiss, S., and Wilkins, R. W.: Nature of the Cardiovascular Disturbance in Vitamin Deficiency States, *Tr. A. Am. Physicians* 50: 45, 1935.
9. Keefer, C. S.: The Beriberi Heart, *Arch. Int. Med.* 45: 1, 1930.
10. Kepler, E. J.: Beriberi from Diet of Raw Starch, *J. A. M. A.* 85: 409, 1925.
11. Lewis, T., and Drury, A. N.: Observations Relating to Arteriovenous Aneurism, Circulatory Manifestations in Clinical Cases With Particular Reference to Arterial Phenomena of Aortic Regurgitation, *Heart* 10: 301, 1923.
12. Holman, E.: Experimental Studies in Arteriovenous Fistula; Blood Volume Variations, *Arch. Surg.* 9: 822, 1924.
13. Eyster, J. A. E.: Cardiac Dilatation and Hypertrophy, *Tr. A. Am. Physicians* 42: 15, 1927.
14. Eyster, J. A. E.: Experimental and Clinical Studies in Cardiac Hypertrophy, *J. A. M. A.* 91: 1881, 1928.
15. Eyster, J. A. E., Meek, W. J., and Hodges, F. J.: Cardiac Changes Subsequent to Experimental Aortic Lesions, *Arch. Int. Med.* 39: 536, 1927.
16. Eyster, J. A. E., and Meek, W. J.: Studies on Venous Pressure, *Am. J. Physiol.* 95: 294, 1930.
17. Walker, J. E.: Reversible Cardiac Enlargement, *J. A. M. A.* 106: 1795, 1936.
18. Rosenblatt, M. B.: Reversible Cardiac Enlargement (Comment on J. E. Walker's article), *J. A. M. A.* 106: 2177, 1936.

CALCAREOUS DISEASE OF THE AORTIC VALVE

A STUDY OF TWO HUNDRED TWENTY-EIGHT CASES*

THOMAS J. DRY, M.B., AND FREDRICK A. WILLIUS, M.D.
ROCHESTER, MINN.

CALCAREOUS disease of the aortic valve was regarded for many years as somewhat of a pathologic curiosity. Since its original description by Mönckeberg,¹ in 1904, there has been much speculation regarding its etiology. Such speculation has found expression, for the most part, in hypotheses postulating either an atherosclerotic²⁻⁵ or an inflammatory origin.⁶⁻⁹ Regarding the latter, both rheumatic and non-rheumatic infections have been incriminated, and the intriguing but unsupported supposition that calcareous disease of the aortic valve represents the healed stage of subacute bacterial endocarditis has been entertained.

There are several important reasons why the earlier investigations of isolated examples or of small groups of cases yielded information which placed calcareous disease of the aortic valve in a category somewhat out of relationship with the conventional and well-recognized forms of cardiac disease. Those reasons were the belief that calcareous disease of the aortic valve was rare, that its distribution as regards sex was peculiar, that its clinical behavior differed in many respects from that of the better known forms of inflammatory heart disease, and, finally, that diagnostic criteria had not been recognized by the clinician until relatively recent years. That a disease characterized by rather dramatic physical signs should have escaped attention even through that phase of the history of diagnosis in which particular heed was paid to cardiac murmurs is quite surprising. Perhaps the one factor which has served as the main stimulus in reviving interest in calcareous disease of the aortic valve has been the development of a fluoroscopic procedure whereby calcified aortic leaflets can be visualized during life (Fig. 1).¹⁰⁻¹⁴ Occasionally, deposition of calcium is sufficiently extensive to permit its demonstration on the roentgenogram (Fig. 1). In this connection it is interesting to note that Christian,⁶ impressed by the marked degree of calcification found in the group of cases which he reported in 1931, predicted the feasibility of demonstrating these calcified leaflets by roentgenologic examination.

Since the review of our material was begun, Clawson, Noble, and Lufkin¹⁵ have published an analysis of 200 cases of calcified aortic valve studied at necropsy. They noted, as have previous writers, its preponderance among males and its high incidence in the older age groups. With

From the Section on Cardiology, the Mayo Clinic.

*Read before the meeting of the American Heart Association, San Francisco, Calif., June 9 and 10, 1938.

Received for publication August 1, 1938.

due emphasis on the pathologic features and possible etiologic factors, their studies indicate that a "history of rheumatism" and stigmas of previous rheumatic infection (namely, deformities of the mitral or other valves, adherent pericardium, presence of Aschoff nodules in the myocardium, microscopic evidence of proliferative inflammation, and presence of blood vessels in the cusps and rings) occurred with almost the same frequency in calcareous disease of the aortic valve as in other healed rheumatic deformities of the valve.



Fig. 1.—Calcareous disease of the aortic valve in which calcification was sufficiently extensive to be demonstrable roentgenographically. This condition usually is demonstrable fluoroscopically only.

In order to avoid confusion, we wish to describe very briefly the essential criteria which have been defined as diagnostic of calcareous stenosis of the aortic valve.⁶ A loud, rough systolic bruit is present over the base of the heart and is conducted into the vessels of the neck and, in many instances, over the entire precordium. The second heart tone is absent or diminished in intensity and, in those cases in which there is an

associated aortic regurgitation, it is replaced by a soft blowing diastolic murmur. A thrill is usually palpable over the upper part of the sternal region. Evidence of cardiac hypertrophy usually can be elicited, and roentgenologic examination reveals the presence of deposits of calcium within the aortic cusps or annulus.

MATERIAL FOR STUDY

In the present study the material at our disposal was arranged in groups for reasons that will become evident. Group 1 consisted of 106 cases of calcareous disease of the aortic valve with data obtained clinically and at necropsy. Group 2 consisted of ninety cases in which all the criteria necessary to permit a clinical diagnosis of calcareous stenosis of the aortic valve were satisfied, and calcification in the leaflets of the valve or in the annulus was demonstrated fluoroscopically. This group represents cases observed in the years 1933 to 1937, inclusive, and is distributed as follows: 1933, four cases; 1934, fourteen cases; 1935, seventeen cases; 1936, thirty-three cases; 1937 (part) twenty-two cases. Group 3 consisted of thirty-two cases of roentgenologically demonstrable calcification of the aortic leaflets, in which, according to the concepts laid down in the earlier literature, not all of the criteria necessary to permit a clinical diagnosis of calcareous stenosis of the aortic valve were satisfied. The main differences between group 3 and group 2 consist of preservation of the second aortic sound in the cases of group 3, which we regarded as indicative of dynamic function of the leaflets, the less constant occurrence of a basal thrill in the cases of group 3, less evidence clinically of cardiac hypertrophy, and, on the whole, fewer cardiac symptoms in the cases of group 3. Because of these differences, these cases, when encountered clinically, were catalogued separately as "calcified aortic valves." But in the light of information subsequently disclosed in the clinicopathologic survey of cases of calcareous disease of the aortic valve in which necropsy was performed, we feel satisfied that these cases should be classified with the second group, and that they represent, as we will show presently, definite but milder degrees of stenosis of the aortic valve (graded 1 and 2 on the basis of 1 to 4) with lesser degrees of calcification of the aortic leaflets; for the sake of clarity, they will be considered separately for the time being.

Controls.—A survey was made of 2,616 consecutive necropsies performed during the period 1933 to 1937, inclusive, to ascertain the incidence of calcareous disease of the aortic valve among all varieties of healed rheumatic valvular disease. There were 127 instances (4.8 per cent of all necropsies) in which some variety of healed valvular defect was found. Of these, twenty-three (18.1 per cent) were found to be calcareous disease of the aortic valve (0.9 per cent of all necropsies).

Review was made of 106 cases of mitral stenosis in the general material obtained at necropsy with reference to history of rheumatic fever, associated valvular involvement, and adherent pericarditis. In 63 per cent

of cases a history of rheumatic fever had been obtained; associated valvular disease was found in 63 per cent, and there was evidence of healed rheumatic pericarditis in 23 per cent.

PATHOLOGIC DATA

Degrees of Stenosis and Calcification of the Aortic Valve.—It was apparent immediately that the degree of stenosis of the aortic valve varied considerably. In eighteen cases the degree of stenosis was extreme (grade 4). In many of these the degree of fusion and calcification of the cusps had reduced the aortic opening to a mere slit (6 to 7 mm. by 2 to 3 mm.) and, in one case, there was complete fusion of all the cusps, a fenestration through one cusp affording the only opening from the left ventricle into the aorta. In forty cases stenosis was marked (grade 3). In forty-five cases stenosis was considered moderate in degree (grade 2). The degree of fusion of the cusps was less marked than in the previous group but, at the same time, the orifice of the aortic valve was diminished definitely in size. Finally, there were three cases in which stenosis was minimal (grade 1), but there was unmistakable evidence of calcification, most marked in the region of the aortic ring.

In order to illustrate clearly the picture of calcareous disease of the aortic valve with minimal stenosis, complete details relative to one of these three cases are presented. A man, aged 68 years at the time of his death in 1937, was first seen at the Mayo Clinic in 1920. In the seventeen years that followed he was examined on many occasions by one of us (F. A. W.). At his first visit it was noted that there was a soft systolic murmur audible at the aortic and mitral areas. He had no cardiac complaints and his blood pressure was 140/74. Four years later he returned and gave a history of short attacks of paroxysmal tachycardia and complained of heart consciousness. The objective manifestations were essentially the same as on previous visits except that the bruit was described as being definitely aortic in situation, and accentuation of the second aortic sound was noted. There was no evidence of diminished tolerance for exercise, and the electrocardiographic examination gave evidence of a rate of 107, sinus tachycardia, and left ventricular preponderance. Several visits in the succeeding nine years disclosed no new features; the only cardiac complaints noted were relative to the patient's consciousness of extrasystoles. The aortic systolic bruit was attributed to aortic sclerosis. In 1935 he returned for a general examination. Apart from palpitation, new cardiac symptoms had not developed, and the physical findings corresponded with those of previous visits. The second aortic sound again was described as distinct and accentuated. On this occasion fluoroscopic examination of the aortic valve was carried out and this revealed calcification of the aortic leaflets. Electrocardiographic examination gave evidence of a rate of 73, sinus rhythm, left ventricular preponderance, and delayed A-V conduction (the P-R interval measured

0.28 second). After the administration of $\frac{1}{100}$ grain (0.0006 gm.) of atropine sulfate subcutaneously, however, the A-V conduction time measured 0.20 second, indicating that the conductive defect previously noted was not caused by organic cardiac disease. The patient's blood pressure was 160/84, and examination of the ocular fundi revealed slight sclerosis of the retinal arteries.

The patient returned in 1937 because of rapid decline in general health, and succumbed to widespread metastasis to bone from sarcoma of the mesentery. Throughout his entire history there was neither significant evidence of limitation of cardiac reserve nor evidence clinically or roentgenologically of much cardiac hypertrophy. At no time was a thrill elicited. At necropsy the heart weighed 420 gm. The aortic leaflets showed definite calcification macroscopically, but not to the extent of rendering the cusp as rigid as in the more advanced degrees of calcification. There was only slight fusion of the margins of the cusps. The coronary arteries, as well as the aorta, were extremely arteriosclerotic, in marked contrast with most of the cases in which there were higher degrees of stenosis of the aortic valve. In summary, this case is an example of comparatively minimal calcareous disease of the aortic valve, with minimal stenosis, presenting physical signs which do not satisfy, for very obvious reasons, all the criteria previously described as diagnostic of calcareous stenosis of the aortic valve. By the same token, the mechanical disadvantage imposed on the left ventricle by the presence of such stenosis is not great enough to result in marked cardiac hypertrophy or in appreciable limitation of cardiac reserve. We wish to emphasize, further, that this lesion was present seventeen years before death and, unquestionably, had its inception many years before the patient first came under our observation.

The degree of calcification, in the majority of cases, paralleled the degree of stenosis (Fig. 2). In some cases, there was an extension of calcification to the ventricular wall, involving secondarily the aortic cusp of the mitral valve and, in three instances, there was extension into the base of the aorta in such a way as to obstruct the orifices of one or both coronary arteries. Interestingly enough, all three patients died suddenly. At times, calcification was disposed in the form of irregular cauliflower-like masses or nodules, suggesting that the calcifying process had effected a stony metamorphosis in a previously inflammatory vegetation, an appearance which, no doubt, suggested the possibility to some investigators that the disease represents the healed stage of subacute bacterial endocarditis.

STIGMAS OF PREVIOUS RHEUMATIC INFECTION (CASES IN WHICH NECROPSY WAS PERFORMED)

History of Rheumatic Fever.—Single or repeated attacks of acute rheumatic fever were recorded in sixteen of the 106 cases.



Fig. 2.—Gross and roentgenographic appearance of varying degrees of stenosis and calcification of the aortic valve. *a*, Stenosis and calcification, grade 1 [note minimal calcification of the aortic ring and leaflets indicated by arrows, and marked calcification in the coronary vessels (a) and aortic arch (b)]; *b*, stenosis and calcification, grade 2; *c*, stenosis and calcification, grade 3; *d*, stenosis and calcification, grade 4.

Associated Valvular Disease.—In many instances there were varying degrees of sclerosis and thickening of the leaflets of the mitral valve, with or without atheromatous plaques. Less frequently these changes were present in the other valves as well. Because they occurred as frequently among other individuals of the same age, no particular significance was attached to these changes. However, when there was shortening or fusion of the chordae tendineae and narrowing of the mitral orifice, we felt that we were dealing with definite evidence of healed rheumatic endocarditis. The degree of mitral stenosis varied from mild degrees to the classical "fish-mouth" type. On this basis, we found mitral stenosis present in fifteen cases, in twelve of which there was a history of rheumatic fever; endocarditis of the mitral and tricuspid valves was found in five cases, in two of which there was a history of rheumatic fever; endocarditis of the mitral, tricuspid and pulmonic valves was found in one case, in which there was also a history of rheumatic fever; and endocarditis of the tricuspid valve was found in one case.

Pericarditis.—In four cases there was an extensive obliterative type of adhesive pericarditis, in two of which there was a history of previous rheumatic fever. There was nothing to indicate that these cases of pericarditis were the result of secondary extension from suppurative disease of the lungs.

In all there were twenty-five cases (23.5 per cent) in which there was definite evidence of associated lesions representing the healed stage of rheumatic infection, a lower incidence than that associated with mitral stenosis (37 per cent).

Weight of Heart.—The weight of the heart in ninety-six of the 105 cases was recorded at necropsy. These weights are presented in Table I. Although no corrections were made for such factors as obesity and associated hypertension, it will be noted that in eighty-two cases (85.5 per cent) the heart weighed more than 400 gm.

TABLE I
WEIGHT OF HEART: NINETY-SIX CASES

HEART WEIGHT, GM.	200-299	300-399	400-499	500-599	600-699	700-799	800-899	900-999	1000+
Cases	1	13	24	25	11	11	7	2	2

Sclerosis of Coronary Vessels and Aorta.—Correlation of the degrees of stenosis and calcification of the aortic valve with the weight of the heart and with the degree of atherosclerosis of the coronary vessels and aorta is presented in Table II. The table is self-explanatory and substantiates again the observation previously made that sclerosis of the aorta and coronary vessels is likely to occur in inverse proportion to the degree of stenosis of the aortic valve. We wish to draw attention, also,

to the relatively short period between the onset of symptoms and final failure, particularly among the cases in which there was an associated mitral endocarditis.

TABLE II

CORRELATION OF DEGREES OF STENOSIS AND CALCIFICATION OF THE AORTIC VALVE WITH WEIGHT OF THE HEART AND WITH DEGREE OF ATHEROSCLEROSIS OF CORONARY VESSELS AND AORTA

CASES	AVERAGE AGE (YR.)	STENOSIS, AORTIC VALVE (GRADE)	CALCIFICATION, AORTIC VALVE (AVERAGE GRADE)	CORONARY SCLEROSIS (AVERAGE GRADE)	SCLEROSIS OF AORTA (AVERAGE GRADE)	WEIGHT HEART, AVERAGE (GM.)	DURATION SYMPTOMS, AVERAGE (YR.)	ASSOCIATED MITRAL ENDOCARDITIS, CASES
18	54.5	4	3+	1+	2	603	3.7	3
40	58.1	3	3+	2	2	526	2.0	14
45	62.6	2	2+	2	2+	477	2.9	9
3	66.0	1	1+	2	2+	428	0	0

Coronary Occlusion.—Acute coronary occlusion was encountered in but one case, and was the cause of death. In another case, there was a healed myocardial infarct. One additional case, that of a woman aged 66 years who had diabetes, requires special comment, in that she had experienced an attack which had all the characteristics of an acute coronary accident, including the classical electrocardiographic pattern and increased sedimentation rate; yet, when necropsy was performed there was no indication that such an event had occurred.

Causes of Death.—The causes of death may be summarized as follows: Thirty-two patients died of congestive heart failure (30.5 per cent). Eighteen patients died suddenly (17.0 per cent). Four of these patients had congestive failure and death occurred while the patient was under treatment. The response of each patient to therapy had been satisfactory up to the time of death. Five patients died of subacute bacterial endocarditis (4.7 per cent), one of acute coronary occlusion (0.9 per cent), and fifty died owing to causes not cardiac in origin (47 per cent).

It is noteworthy that, of the twenty-six patients who had associated mitral disease, the death of twenty-one patients (81 per cent) could be attributed directly or indirectly to the cardiac disease present. Thus, eleven patients died of congestive failure, five died suddenly, three died as a result of embolic phenomena, and two of superimposed subacute bacterial endocarditis.

It is also of interest to note that the majority of patients who died when the syndrome of congestive heart failure was present responded to therapy in a rather disappointing manner, compared with the response obtained from those who had congestive failure due to other causes. Symptoms are likely to remain in abeyance for many years, but with the

onset of myocardial failure the outlook becomes serious. One other aspect which influences prognosis considerably is the high incidence of sudden death of patients who frequently present little, if any, evidence of heart disease. In an attempt to gain further information with regard to the type of patient who is likely to die suddenly, we have analyzed critically the data relative to this group of cases, the details of which are presented in Table III.

TABLE III
PATIENTS WHO DIED SUDDENLY

NUM- BER	AGE, YEARS AND SEX	POST-MORTEM FINDINGS				REMARKS
		STENOSIS, GRADE	CALCIFICATION, GRADE	WEIGHT OF HEART, GM.	CORONARY SCLEROSIS, GRADE	
1	63 M	3	3	586	3	Apparently good health
2	54 M	4	4	543	3	History of syn- copal attacks
3	53 M	3+	3	520	3	Recent uneventful abdominal opera- tion
4	62 M	4	4	646	-	History of angina pectoris
5	38 M	4	4	565	2	Apparently good health
6	79 M	3	4	740	4	Previous history not available
7	71 M	4	4	600	3	Healed infarcts; history of angina
8	57 F	3+	3+	x2	0	Dyspnea on exer- tion for one year
9	64 M	3+	3+	470	2	History of angina
10	64 M	3+	4	821	2	Calcification of aortic valve ex- tended to coro- nary orifices.
11	29 F	4	4	573	0	Number 10 gave a history of an- gina pectoris
12	46 M	2+	4	970	0	
13*	45 F	2+	2+	360	2	
14	72 F	3+	3+	531	3+	Was being treated for congestive heart failure and was responding well to treatment before death
15†	46 M	3+	3+	892	1+	
16*	42 F	3+	3	655	0	
17	75 M	2	2+	550	3	Calculus of bladder removed six weeks before death
18*	56 F	3	3	434	1+	Thyroidectomy performed; doing well before death

*Associated mitral stenosis.

†Adhesive pericarditis obliterating two-thirds of pericardial cavity.

We wish to draw attention to the following facts arising from this analysis. 1. Fifteen of the eighteen patients who died suddenly had a marked degree of stenosis and calcification of the aortic valve. 2. In fourteen of the eighteen subjects, the heart weighed more than 500 gm., and in one other it was described as being twice the normal size. 3. Acute myocardial infarction was not responsible for the death of any of these patients. 4. Seven patients had severe coronary sclerosis. 5. Four patients gave a history of angina pectoris. 6. Three patients are of unusual interest in that, although coronary sclerosis was minimal or entirely absent, calcification of the aortic valve had extended to the region of the coronary ostia and was causing partial obstruction to flow of blood in the coronary vessels. Up to the time of their unexpected and sudden death, these patients had pursued their respective occupations. One of them gave a history of angina pectoris but others gave little, if any, history suggestive of much limitation of cardiac reserve.

CLINICAL DATA

Distribution According to Sex.—Group 1 was composed of eighty-eight men and eighteen women; group 2 was composed of sixty-eight men and twenty-two women; group 3 was composed of twenty-seven men and five women. In all, there were 183 men and forty-five women, a ratio of 4:1.

Distribution According to Age.—In group 1 (106 subjects on whom necropsy was performed), ages ranged from 22 to 87 years; the average was 58.8 years. The average age of the men was 63.4 years, ranging from 22 to 87 years. The average age of the women was 43.2 years, ranging from 29 to 72 years. The distribution by decades is illustrated in Table IV.

TABLE IV
DISTRIBUTION ACCORDING TO AGE

AGE	GROUP 1			GROUP 2			GROUP 3		
	TOTAL	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL	MALE	FEMALE
20-29	3	2	1	4	2	2	0	0	0
30-39	5	4	1	12	8	4	2	1	1
40-49	20	16	4	15	12	3	3	2	1
50-59	24	19	5	24	18	6	11	10	1
60-69	30	24	6	20	17	3	12	11	1
70-79	20	19	1	14	10	4	4	3	1
80-89	5	5	0	1	1	0	0	0	0
Totals	106	88	18	90	68	22	32	27	5
Average total	58.8			53.6			59.4		
Average males	63.4			54.0			60.0		
Average females	43.2			51.4			56.4		

In group 2 (ninety patients studied clinically with confirmation of the diagnosis by fluoroscopic examination), the ages ranged from 23 to 86 years; the average was 53.6 years. The average age of the men was 54

years, ranging from 25 to 86 years. The average age of the women was 51.4 years, ranging from 23 to 78 years. The distribution by decades is illustrated in Table IV.

In group 3 (thirty patients studied clinically with confirmation of the diagnosis by fluoroscopic examination, but with findings on physical examination which were atypical), ages ranged from 38 to 78 years; the average was 59.4 years. The average age of the men was 60 years, ranging from 38 years to 72 years. The average age of the women, as in the other groups, was lower than that of the men, 56.4 years, ranging from 38 to 78 years. The distribution by decades is illustrated in Table IV.

STIGMAS OF PREVIOUS RHEUMATIC INFECTION (CLINICAL CASES)

Previous Rheumatic Infection.—Thirty patients belonging to group 2 and four patients belonging to group 3 gave a history of rheumatic fever. Together with the sixteen subjects belonging to the group on whom necropsy was performed, there were fifty patients in all (22 per cent) who had given a history of rheumatic fever.

Associated Valvular Disease.—Already we have mentioned that evidence of healed rheumatic lesions of one kind or another was found at necropsy in 23.5 per cent of cases of calcareous disease of the aortic valve. In group 2, a clinical diagnosis of associated mitral stenosis was made in six instances. Examination of three of these fluoroscopically gave evidence of calcification of mitral leaflets, although in three additional cases there was also fluoroscopic evidence of mitral calcification. Calcification of the mitral valve also was demonstrated fluoroscopically in two cases belonging to group 3.

Symptoms and Signs.—One of the striking features of the group as a whole is the insidiousness with which cardiac hypertrophy can reach gross proportions with little or no evidence clinically of interference with myocardial efficiency. This can only mean that the process of stenosis develops very gradually and that myocardial nutrition is maintained by an adequate coronary circulation. Our findings substantiate such a premise very strongly, and the clinical records reveal numerous instances of long-standing valvular disease in which the bruits discovered in earlier and repeated examinations corresponded with those which, years later, proved to be the result of calcareous disease of the aortic valve. Furthermore, there are instances in which the information was less accurate but in which the known presence of murmurs had covered a period of many years, in some cases, forty years or more.

When symptoms do arise, they are essentially those of myocardial insufficiency or of coronary insufficiency, a circumstance determined more by the process of stenosis than by associated disease of the coronary vessels and, as has been pointed out previously, the onset of symptoms in the majority of instances ushered in the final stages of the disease.

In Table V, the incidence of the individual symptoms is presented. It is to be recalled that group 1 is comprised of cases of all degrees of stenosis, that group 2 consists of cases in which there was clinical evidence of the more marked degrees of stenosis, whereas in group 3 there is reason to believe that we were dealing with less marked degrees of stenosis and, hence, we observed milder symptomatology and less typical physical findings. It will be noted that dyspnea was the most notable symptom indicative of a failing myocardium. Angina pectoris, when it occurred, was angina of effort, and in no instance did we encounter the prolonged type of anginal seizures which occur at rest among some individuals who are the victims of aortic insufficiency. The details regarding cases in which angina pectoris was a symptom are given in Table VI.

TABLE V
INCIDENCE OF SYMPTOMS

	GROUP 1, PERCENTAGE	GROUP 2, PERCENTAGE	GROUP 3, PERCENTAGE
No symptoms	29.1	21.4	50.0
Dyspnea	70.4	83.3	40.1
Angina pectoris	15.2	24.4	18.7
Syncope or vertigo	7.6	10.0	9.4
Congestive failure	32.4	31.1	12.5
Uncertain	6.6	2.2	9.4

Vertigo and syncope (at times epileptiform in character) were encountered infrequently and, in some, these manifestations were provoked by exercise, even in the absence of heart block.

The characteristic bruit and thrill associated with well developed calcareous stenosis of the aortic valve need no further description here; it is well known that, in addition, a regurgitant aortic murmur frequently is present. In our series an aortic diastolic murmur was recorded twenty-seven times in group 1, forty-eight times in group 2 and four times in group 3, that this, in 35 per cent of the entire series studied. This murmur is likely to be low-pitched, soft, and not easily audible. It is quite probable that in the earlier series comprising group 1 the diastolic murmur was present more frequently than the records indicate. It is not uncommon to find some variation in the intensity of the physical signs, particularly in the presence of a failing myocardium; among individuals who have emphysema the signs also may be obscured. Usually, both murmurs and thrills can be elicited more readily during full expiration with the patient leaning forward or after cardiac activity has been increased by gentle exercise.

Considerable attention rightly has been paid to the nature of the second aortic sound. From our clinicopathologic correlations, however, we feel certain that definite stenosis can be present when the second aortic sound is normal in character. When absent or considerably reduced, it can be concluded safely that the degree of stenosis is considerably advanced.

TABLE VI
CASES IN WHICH ANGINA PECTORIS WAS A SYMPTOM
DATA OBTAINED AT NECROPSY

NUMBER	AGE, YEARS AND SEX	CORONARY SCLEROSIS, GRADE	STENOSIS, GRADE	WEIGHT OF HEART, GM.	AORTIC REGURGITA- TION	CAUSE OR NATURE OF DEATH
1	64 M	2	2	470	0	Sudden
2	31 M	—	2+	700	+	Congestive fail- ure
3	69 M	4	3	500	0	Congestive fail- ure
4	58 M	3	2	1170	+	Congestive fail- ure
5	64 M	2	3	821	0	Sudden
6	62 M	—	4	646	0	Sudden
7	74 M	2	2	428	0	Congestive fail- ure
8	63 M	1+	3	611	+	Congestive fail- ure
9	54 M	1	2	778	0	Uremia (hyper- tension)
10	79 M	3	4	480	0	Congestive fail- ure
11	55 M	4	3	875	0	Congestive fail- ure
12	76 M	1	3+	517	0	Postoperative prostatectomy
13*	65 F	3+	2	449	0	Diabetic gan- grene
14	49 M	1	2	510	+	Congestive fail- ure
15	56 M	3+	3	538	0	Coronary occlu- sion
16†	59 M	3	4	600	0	Sudden

*Symptoms and signs of acute coronary occlusion developed; not confirmed at necropsy.

†Healed infarct.

Size of the Heart.—The most eloquent expression of the almost constant presence of cardiac hypertrophy is afforded by 96 per cent of the subjects on whom necropsy was performed and the weight of the heart recorded. Remembering that stenosis varied from the mildest to the most extreme degree, it is of interest to note that in 85.5 per cent of the cases the heart weighed more than 400 gm. The term "heavy heart"¹⁶ which has been applied in the description of these cases is very appropriate. There was definite clinical evidence of cardiac hypertrophy in sixty-eight of the ninety cases in group 2 and in seventeen of the thirty-two cases in group 3.

Electrocardiographic Findings.—In group 1, an electrocardiogram was recorded in sixty-three cases, in group 2 it was recorded in eighty-three cases, and in group 3 in twenty-eight cases. Thus, there was a total of 174 records for analysis. The details of this analysis are shown in Tables VII, VIII, IX, and X. The composite of Tables VII, VIII, IX, and X, and, thus, of the electrocardiographic findings as a whole, is shown in Table XI.

TABLE VII
ELECTROCARDIOGRAPHIC FINDINGS
NO SIGNIFICANT CHANGES IN T-WAVE

	GROUP 1	GROUP 2	GROUP 3	TOTAL
Number of cases	23	29	18	70
Regular rhythm	17	26	17	60
Auricular fibrillation	6	3	1	10
Left axis deviation	15	16	11	42
Right axis deviation	3	0	1 (sl.)	4
No preponderance	5	13	6	24
Delayed A-V conduction	2	1	0	3
Complete heart block	1	1	0	2
Bundle branch block	0	1	0	1

TABLE VIII
ELECTROCARDIOGRAPHIC FINDINGS
T-WAVE NEGATIVITY IN LEAD I OR IN LEADS I AND II (INCLUDING
DIPHASIC T-WAVES)

	GROUP 1	GROUP 2	GROUP 3	TOTAL
Number of cases	23	29	7	59
Regular rhythm	19	23	7	49
Auricular fibrillation	4	6	0	10
Left axis deviation	20	24	4	48
Right axis deviation	0	0	1 (sl.)	1
No preponderance	3	5	2	10
Delayed A-V conduction	2	1	2	5
Complete heart block	0	2	0	2
Bundle branch block	2	5	1	8

TABLE IX
ELECTROCARDIOGRAPHIC FINDINGS
T-WAVE NEGATIVITY IN LEADS I, II, AND III (INCLUDING DIPHASIC T-WAVES)

	GROUP 1	GROUP 2	GROUP 3	TOTAL
Number of cases	10	16	1	27
Regular rhythm	9	15	1	25
Auricular fibrillation	1	1	0	2
Left axis deviation	4	4	0	8
Right axis deviation	0	2 (sl.)	0	2
No preponderance	6	10	1	17
Delayed A-V conduction	0	3	0	3
Complete heart block	0	0	0	0
Bundle branch block	1	0	0	1

TABLE X
ELECTROCARDIOGRAPHIC FINDINGS
T-WAVE NEGATIVITY IN LEADS II AND III (INCLUDING DIPHASIC T-WAVES)

	GROUP 1	GROUP 2	GROUP 3	TOTAL
Number of cases	7	9	2	18
Regular rhythm	6	7	2	15
Auricular fibrillation	1	2	0	3
Left axis deviation	2	1	1	4
Right axis deviation	4	2	0	6
No preponderance	1	6	1	8
Delayed A-V conduction	1	1	0	2
Complete heart block	0	0	0	0
Bundle branch block	0	0	0	0

TABLE XI

SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS, 174 CASES*

	CASES	PER CENT	REMARKS
Regular rhythm	149	85	
Auricular fibrillation	25	15	In one case, auricular flutter alternated with auricular fibrillation
Left axis deviation	102	58.6	
Right axis deviation	27	15.5	
No preponderance	59	34	
No significant changes in T-wave	70	40.2	
Inversion of T-wave in Lead I or in Leads I and II	59	34	Including diphasic T-waves
Inversion of T-wave in Leads I, II, and III	27	15.5	Including diphasic T-waves
Inversion of T-wave in Leads II and III	18	10.3	Including diphasic T-waves
Disturbance of conduction	27	15.5	

*Composite of Tables VII, VIII, IX, and X.

Critical analysis of these electrocardiographic findings shows that they conform essentially to patterns consistent with established physical laws of electrocardiography. In short, an aortic lesion throws added strain on the left ventricle and, in most cases, this is indicated in the electrocardiogram by left axis deviation, and, should changes in the T-wave occur, Lead I or Leads I and II will be affected.¹⁶

Of special interest are the other cases in which, despite the presence of a mechanism capable of producing left ventricular strain and the conventional changes in the T-waves mentioned, there were changes either in all three leads or in Leads II and III. The latter group is dismissed easily, for we find that in the seven cases in which necropsy was performed and in which changes in the T-wave had occurred in Leads II and III, a complicating factor consistent with such a pattern was present in six. Thus, in four cases there was an associated mitral stenosis, and in one there was an advanced degree of pulmonary arteriolar sclerosis. The fact that the electrocardiograms of four of the five patients mentioned gave evidence also of right axis deviation confirms the contention that, in the differential effect on the two ventricles, right ventricular strain predominated. The electrocardiogram of the fifth patient gave evidence of left axis deviation, but he had taken digitalis to the point of vomiting and the changes in the T-wave in the second and third leads were undoubtedly the result of intoxication by digitalis. The sixth patient died as a result of extensive infarction involving the lateral wall of the left ventricle. There was also a healed infarct in the posterior basal portion of the left ventricle, providing again adequate explanation of the resulting electrocardiographic pattern. There are two records available in the seventh case. The first showed inversion of the T-wave in Lead III only, whereas in a second electrocardiogram, taken a few weeks later, the T-waves in both the second and third leads were inverted. This patient died as a result of widespread metastasis from carcinoma of the thyroid gland, but there was no evidence of metastatic involvement of the heart.

We were interested in studying the differential effect on the two ventricles caused by lesions involving both the aortic and mitral valves, including the cases of mitral stenosis associated with tricuspid endocarditis. There were twenty-two such records among the group of cases in which necropsy was performed. On electrocardiographic examination, left axis deviation had been noted in thirteen of these, of which seven showed changes in the T-wave in Lead I or in Leads I and II and only two showed changes in the T-wave in Leads II and III, one of which was the case already mentioned in which overdigitalization had occurred. In none of these thirteen cases was auricular fibrillation present. Right axis deviation had been noted in two cases, in both of which there was inversion of the T-wave in Leads II and III, conforming again to recognized laws of electrocardiographic behavior. In the remaining seven cases neither ventricle showed preponderance, and changes in the T-wave followed no special pattern. It is noteworthy that auricular fibrillation, which had occurred in five cases, was associated with either right axis deviation or with no preponderance of either ventricle, except in one case; this suggests that, as long as the left ventricle carries the major load, the auricles are far less likely to fibrillate than when the reverse is true.

In considering the ten cases in which necropsy was performed and in which changes in the T-wave had affected all three leads, mitral stenosis was present in four cases, and in one of these there was extensive adhesive pericarditis. In the remaining six cases there were no additional factors found which might have influenced the pattern of the T-wave. In this group of ten cases left axis deviation had been noted in only two; the remaining ones gave no evidence of preponderance of either ventricle.

Blood Pressure.—It has been commented on previously that the blood pressure seldom is elevated in this disease and that the pulse pressure is low, reflecting the effect of stenosis of the aortic orifice. Although this is essentially true in many instances, a survey of a large group of cases shows much variation in the height of both systolic blood pressure and pulse pressure; hypertension and aortic regurgitation constitute the main reasons for this variability. Differential analysis of blood pressure readings in the various groups which constitute our series is of interest. Thus, in group 1, which is composed of cases of all grades of aortic stenosis, the blood pressure of 38 per cent of the subjects had been more than 150 mm. Hg systolic or more than 90 mm. diastolic, and the readings of 62 per cent had been lower than these figures. In only three instances was the systolic blood pressure more than 200 mm. Hg. In correlating the blood pressure with the degree of stenosis, it is of interest to note that the average degree of stenosis in those cases in which high readings had been obtained was graded 2 (on the basis of 1 to 4) and, in 50 per cent of cases, the stenosis was graded 3 and 4 (but actually only three cases were graded 4), as compared with the average stenosis, graded 3,

in those cases in which low readings were obtained; in 66.6 per cent of these cases the stenosis was graded 3 and 4 (thirteen of which were graded 4).

In group 2, presenting clinical evidence of the more marked degrees of stenosis of the aortic valve, only 23 per cent had blood pressure readings higher than 150 mm. Hg systolic or 90 mm. diastolic, whereas 77 per cent had readings lower than these. In only two instances (2.2 per cent) was the systolic blood pressure found to be higher than 200 mm. Hg.

Finally, of the patients of group 3 (presenting clinical evidence of a lesser degree of stenosis of the aortic valve than that of group 2), fully 50 per cent had blood pressure readings higher than 150 mm. Hg systolic or 90 mm. diastolic, and three patients (10 per cent) had a systolic pressure higher than 200 mm. Hg.

It seems, therefore, that blood pressure is influenced, in a measure, by the degree of stenosis of the aortic valve, and that the height of the blood pressure bears an indirect relationship to the degree of stenosis of the aortic valve present, although it must be pointed out that, even if an extreme degree of stenosis of the aortic valve exists (confirmed at autopsy), it is possible to have severe forms of hypertension and all the associated changes in the peripheral vascular system that occur in cases of hypertension unassociated with disease of the aortic valve.

DISCUSSION

The evidence derived from the study of this material has led us to accept, unequivocally, rheumatic infection as the etiologic factor in calcareous stenosis of the aortic valve. During recent years, considerable confusion has resulted from the belief that stenosis of the aortic valve represented two types of lesions: the one identified as the rheumatic type, the other as the calcareous type. It is not without significance that, in the review of our complete material obtained at necropsy, no instance of stenosis of the aortic valve without some degree of calcification was encountered. The lesion does occur in young individuals who give a history of rheumatic fever and it occurs in association with mitral stenosis, a pathologic entity universally accepted as an unquestionable stigma of previous rheumatic infection, and indeed the incidence of single or repeated episodes of rheumatic fever, as revealed in the history of those who have a solitary lesion of the aortic valve, occurs far too frequently to represent merely a coincidence.

We must draw attention to the fact that both in Christian's group of twenty-one cases and in the group of forty-two cases reported by Margolis and others,¹⁷ only hearts which on examination did not show evidence of associated valvular disease were accepted for study, and it is obvious that, in this discriminate selection, the very cases which bear the appropriate etiologic label (in the form of healed mitral endocarditis) were excluded from their respective series. Both of these

studies were made in 1931, before the knowledge on which much of this paper is based was available. Christian's contention, nevertheless, was that the disease was of rheumatic origin.

That deposition of calcium should occur in a region of low vascularity, from which inflammatory products cannot be absorbed adequately, is an expression of the phenomenon of calcification in general. The leaflets of the heart valves satisfy this set of circumstances perfectly.

There are several apparent objections to such an explanation. Firstly, it may be argued, why does not calcification occur universally in all healed rheumatic lesions? And secondly, why does the striking discrepancy as regards sex occur if rheumatic fever attacks both sexes without any appreciable discrimination? Or again, why should the clinical manifestations and the life history of calcareous disease of the aortic valve diverge so widely from those of the conventional forms of rheumatic carditis? The fact that it differs in its clinical behavior, in many respects, from the more classical varieties of rheumatic heart disease is not an argument against its rheumatic origin. Every other smouldering form of chronic inflammatory disease, such as tuberculosis and syphilis, is associated with the same variability in its clinical course as well as in its predilection for certain tissue, which varies from case to case. We wish to present an hypothesis which answers these questions. It is based on the belief that rheumatic infection which culminates in calcareous disease of the aortic valve differs only in a quantitative manner, and not in any qualitative manner, from other types of rheumatic carditis.

Rheumatic infection which eventually culminates in calcareous stenosis of the aortic valve was originally a mild form of rheumatic carditis which had allowed both the mitral valve and the myocardium to escape with minimal or no damage. By the same token, we must assume that although the incidence of rheumatic fever is more or less equal in the two sexes women do not share the same relative immunity to more serious and widespread involvement as often as men. The gradual sclerosing process characteristic of rheumatic valvulitis which follows, and fusion of the cusps, which is part and parcel of the inflammatory reaction, have now set the stage for a very gradually developing stenotic process, a condition which satisfies the pathologic requisites for a similar, gradually progressing deposition of calcium. In the study carried out by Clawson and his co-workers, 84 per cent of all nonsyphilitic deformities of the aortic valve were found to contain calcium on gross examination.

Thus time and a relatively efficient coronary circulation (in the early stages, at least) are the main factors which allow cardiac hypertrophy to proceed so surreptitiously that a heart of 800 gm. is found unexpectedly in a patient dying from an unrelated disease whose previous history revealed little, if any, evidence of limitation of cardiac reserve. It is

this factor of time which explains why calcification need not be a universal concomitant of healed rheumatic lesions, because those harboring the more serious forms of the disease, especially when accompanied by mitral stenosis, are weeded out by death before such an event as calcification can occur, thus leaving the solitary aortic lesion, one that the heart tolerates far better than mitral stenosis,¹⁸ to continue for a long time without embarrassing the cardiac reserve.

Finally, the very fact that a history of rheumatic fever cannot be elicited more frequently than in 22 per cent of cases substantiates the hypothesis that the original acute inflammatory episode was mild and, perhaps, was so atypical that its significance could not have been realized at the time of its occurrence.

Our material was derived largely from the middle western states where conditions are relatively less favorable for the occurrence of rheumatic fever and where, on the whole, mild and atypical forms of the disease may be anticipated. It is possible that surveys in regions where the disease is more prevalent may show a relatively lower incidence of calcareous disease of the aortic valve.

SUMMARY

Calcareous disease of the aortic valve is not rare. We found that it constituted 18.1 per cent of all healed valvular defects. The criteria heretofore outlined for clinical recognition of calcareous stenosis of the aortic valve apply only to the advanced forms of the disease. However, the physical signs of even minimal and moderate degrees of calcareous stenosis and calcification of the aortic valve are sufficiently clearly defined to allow of clinical recognition, especially because it is possible to obtain confirmation by expert fluoroscopic means during the life of the patient. The frequency with which a history of rheumatic fever is obtained and stigmas of rheumatic infection are found is too great to be regarded merely as a casual and not a causative factor. There is convincing evidence that the lesion may be present in a clinically recognizable form for many years. Its very gradual progression, however, speaks for an initially mild valvulitis with even less involvement of the myocardium and of the other valves. Cardiac hypertrophy is present in a high percentage of cases and closely parallels the degree of aortic stenosis. Atherosclerosis of the coronary vessels and aorta occurs in inverse proportion to the degree of stenosis of the aortic valve, and coronary occlusion is extremely rare. Angina pectoris, however, is frequently a symptom and seems to depend more on the stenotic process than on coronary sclerosis.

Death is associated with congestive failure in about a third of the cases. Sudden death occurs in about a fifth of the cases and, in considering all grades of stenosis, death results from noncardiac causes in about half of the cases. The presence of mitral stenosis seriously mili-

tates against maintenance of cardiac function. The more mitral stenosis plays a part, the closer will the case conform to the more conventional forms of rheumatic heart disease. Blood pressure and pulse pressure readings need not be low. Well-recognized laws of electrocardiographic behavior determine the electrocardiographic pattern in calcareous disease of the aortic valve. Auricular fibrillation is relatively rare when the electrocardiogram gives evidence of predominance of the left ventricle.

The prognosis varies considerably, depending largely on the degree of stenosis and on the presence of complicating factors, especially mitral stenosis. Absence of the second aortic sound usually means that marked stenosis exists.

REFERENCES

1. Mönckeberg, J. G.: Der normale histologische Bau und die Sklerose der Aortenklappen, *Virehows Arch. f. path. Anat.* 176: 472, 1904.
2. Libman, E.: Some General Considerations Concerning the Affections of the Valves of the Heart, *M. Clin. North America* 1: 573, 1917.
3. Ribbert, Hugo: Die Atherosklerose der Klappen und des Wandendokards. From Henke and Lubarsch's "Handbuch der speziellen pathologischen Anatomie und Histologie," Vol. 2, p. 195, Berlin, 1924, Julius Springer.
4. Geerling, J. G.: Quoted by Solval, A. R., and Gross, Louis.
5. Solval, A. R., and Gross, Louis: Calcific Sclerosis of the Aortic Valve (Mönckeberg Type), *Arch. Path.* 22: 477, 1936.
6. Christian, H. A.: Aortic Stenosis With Calcification of the Cusps, *J. A. M. A.* 97: 158, 1931.
7. McGinn, Sylvester, and White, P. D.: Clinical Observations on Aortic Stenosis, *Am. J. M. Sc.* 188: 1, 1934.
8. Boas, E. P.: Angina Pectoris and Heart Block, as Symptoms of Calcareous Aortic Stenosis, *Am. J. M. Sc.* 190: 376, 1935.
9. Contratto, A. W., and Levine, S. A.: Aortic Stenosis With Special Reference to Angina Pectoris and Syncope, *Ann. Int. Med.* 10: 1636, 1937.
10. Cutler, E. C., and Sosman, M. C.: Calcification in the Heart and Pericardium, *Am. J. Roentgenol.* 12: 312, 1924.
11. Fleischner, F.: Verkalkung des Annulus fibrosus, *Wien. med. Wchnschr.* 75: 2721, 1925.
12. Parade, C. W., and Kuhlmann, F.: Verkalkungen des Herzskeletts im Röntgenbild, *München. med. Wchnschr.* 1: 99, 1933.
13. Sosman, M. C., and Wosika, P. H.: Calcification in Aortic and Mitral Valves: With a Report of Twenty-Three Cases Demonstrated in Vivo by the Roentgen Ray, *Am. J. Roentgenol.* 30: 328, 1933.
14. Willius, F. A., and Camp, J. D.: Clinical and Roentgenologic Comments on Calcareous Aortic Stenosis, *M. Clin. North America* 19: 487, 1935.
15. Clawson, B. J., Noble, J. F., and Luffin, N. H.: The Calcified Nodular Deformity of the Aortic Valve, *AM. HEART J.* 15: 58, 1938.
16. Barnes, A. R., and Whitten, M. B.: Study of T-wave Negativity in Predominant Ventricular Strain, *AM. HEART J.* 5: 14, 1929.
17. Margolis, H. M., Ziellissen, F. O., and Barnes, A. R.: Calcareous Aortic Valvular Disease. *AM. HEART J.* 6: 349, 1931.
18. Willius, F. A.: A Study of the Course of Rheumatic Heart Disease. *AM. HEART J.* 3: 139, 1927.

AN EVALUATION OF HEART VOLUME DETERMINATIONS BY THE ROHRER-KAHLSTORF FORMULA AS A CLINICAL METHOD OF MEASURING HEART SIZE

WILFRID J. COMEAU, M.D., AND PAUL D. WHITE, M.D.
BOSTON, MASS.

FOR some years roentgenologists, particularly in Italy and Germany, have been interested in clinical methods of cardiac measurement by which heart size might be determined more accurately than by the standard methods of the cardiothoracic ratio or the area of the frontal silhouette. It is agreed that the theoretical ideal for estimating the size of the heart is by determining its volume. Both the cardiothoracic ratio and the frontal cardiac area are measurements limited to one plane, while reliable volumetric determinations require measurements in at least two planes and theoretically should give a better concept of heart size. The clinical possibilities of such a method have received little attention either in this country or abroad and, consequently, it seemed desirable to evaluate the practical application of volumetric estimations of heart size in order to determine whether such a method would offer any advantage to the clinician over the present routine roentgenographic measurements of the heart.

MATERIAL

The material upon which this study is based consists of 100 adult males and seventy adult females with clinically normal hearts and forty individuals with heart disease. The normal material was gathered from ambulatory patients in either the medical or surgical wards or the outpatient department of the Massachusetts General Hospital and from a group of healthy subjects. The majority of the hospital patients were in a good state of general health. Since the age in the normal group ranged from the second through the sixth decades of life, and since electrocardiograms were not taken routinely, it is possible that some of the older individuals may have had slight, unrecognized coronary disease, but none had any symptomatic or physical evidence of heart disease. The group with abnormal hearts consisted mainly of individuals with the more common cardiac lesions.

METHOD

Reconstruction of the heart in plastic material from orthodiographic tracings taken in different planes is unquestionably the most accurate method of determining heart size, the volume of the heart being measured by water displacement of the model. The technique for this procedure has been described by Palmieri.¹ Accurate as this method may be, it is obviously impractical for clinical use.

The alternative is a mathematical formula, of which several have been devised.²⁻⁶ In this study we have employed a formula first described by Rohrer,⁵ in 1916, and, interestingly enough, again independently by Kahlstorf,⁴ in 1932.

From the Cardiac Clinic and Laboratory of the Massachusetts General Hospital, Boston.

Received for publication Sept. 3, 1938.

The theoretical basis for the formula rests in the fact that the shape of the heart in general can be considered to be halfway between that of a paraboloid and an ellipsoid. The volume of these bodies can be determined mathematically with an error of ± 4 per cent by the following formulas: ellipsoid, $V = A \times D \times c$ (0.667); paraboloid, $V = A \times D \times c$ (0.59). A is the surface area of a parallel projection of the body being studied; D , greatest depth diameter in the direction of projection; c , constant.*

Transferring these formulas to the heart, the heart volume can then be approximated by the product of the area of the frontal cardiac silhouette and the greatest horizontal depth of the heart in the lateral position, multiplied by a constant. For the heart this constant would be theoretically halfway between those for the paraboloid and the ellipsoid, i.e., 0.63. In practice this constant may be varied in either direction, as the shape of the individual heart resembles more closely either the ellipsoid or the paraboloid. In this study, however, we have not complicated matters by introducing such an individual variable and have employed only the constant 0.63.

The teleoroentgenographic apparatus to be described in the *AMERICAN HEART JOURNAL*, by Liljestrand, Lysholm, Nylin, and Zachrisson for obtaining the measurements necessary to calculate the heart volume should give slightly more constant results than fluoroscopic measurements. The construction of such an apparatus, however, is hardly practical except for purely experimental purposes. Since we were interested in the practical application of the heart volume formula, we have employed orthodiagraphic measurements. The technical procedure for obtaining these measurements follows.

The individual was seated and the frontal orthodiagram was made in the usual manner. The subject was then rotated 90° to the left and both hands placed on the head. The lateral silhouette of the heart, in so far as it was possible with any degree of accuracy, and the ventral aspect of the sternum were then traced. The esophagus was filled with barium in some cases to help locate the posterior border of the heart. Three separate tracings were made in this position for reasons to be discussed later. The cardiac silhouette of the frontal orthodiagraphic tracing was then completed and the area computed in square centimeters with a planimeter until two determinations checked closely. The greatest horizontal depth diameter was measured in centimeters and the average of the three separate determinations was taken as the depth measurement. The heart volume was not estimated in instances where great discrepancies (over 6 mm.) existed between individual depth measurements. Orthodiascopy was employed exclusively, and the entire procedure from the beginning of fluoroscopy to the computation of the heart volume consumed approximately 15 minutes. The heights of the subjects, without shoes, were determined in centimeters and their weights, with the heavier articles of clothing removed, in kilograms. All percentages in the tables were computed to the nearest significant number and in such a way that the maximum percentage variation would be obtained.

SOURCES OF ERROR IN THE METHOD

Benedetti and Bollini^{7, 8} have discussed volumetric formulas other than their own from the anthropometric standpoint; the main objection to formulas other than that of Bollini is that they do not take into consideration the position of the heart in the thoracic cage as a factor influencing the shape of the heart shadow. There is no doubt that the formula of

*The following abbreviations are used in the tables. A , frontal cardiac area. D , greatest horizontal depth diameter of the heart in the lateral position. V , cardiac volume. T , transverse diameter of the heart. Th , transverse diameter of the thorax. CTR , cardiothoracic ratio.

Bollini³ has been more carefully controlled by comparisons with the actual volume of models and gives theoretically a more accurate estimation of the actual heart volume. We considered, however, that the technical difficulties and errors entailed in tracing accurately the complete lateral silhouette of the heart and in determining the point of bifurcation of the trachea necessary for this formula made this method less suitable and not significantly more accurate in practical application than the simpler Rohrer-Kahlstorf formula. Before discussing the technical errors of the Rohrer-Kahlstorf method, which has been our principal interest, we wish to bring out two objections which apply more or less generally to all mathematical formulas for estimating heart volume.

Firstly, the heart varies so in shape normally that no one mathematical formula can be expected to be generally applicable and to allow an accurate determination of the volume of the heart actually to be measured. While Bollini has in part compensated for this variable by considering the position of the heart in the thorax, there still exist exceptions wherein his formula would be in considerable error. Secondly, it is well known that in heart disease there is very often a predominant enlargement of one chamber of the heart, most commonly the left ventricle or the left auricle. Mathematical formulas in general must consider the heart as a whole, and do not allow for the disproportionate enlargement which takes place in heart disease. It is obvious that such disproportionate enlargement may so affect the necessary orthodiagraphic measurements that they are not justifiably applicable in a method which is theoretically based on a concept of the heart as a more or less uniform geometrical body. For example, in mitral stenosis the enlargement of one chamber, the left auricle, can markedly increase the depth diameter so that a significant error may easily result in the application of such a formula.

Both Rohrer and Kahlstorf placed the maximum error in the formula at ± 15 per cent. Kahlstorf orthodiagraphed formalin-fixed anatomic specimens and compared the volumetric estimation by formula to the volume by water displacement of the specimen. On the results from nine normal and three pathologic hearts he concluded that the maximum error inherent in the formula was ± 5 per cent. Bollini, using heart models made by Palmieri's method and comparing the calculated results by the Rohrer-Kahlstorf method to that by water displacement of the model, found the error to vary from -1 per cent to $+16$ per cent in twenty normals and from $+4$ per cent to $+42$ per cent in ten pathologic hearts. From these figures it is obvious that the error may be negligible or, on the other hand, so great, particularly in diseased hearts, as to invalidate the determination.

Kahlstorf further concluded that maximum additional technical errors of ± 5 per cent each resulted from the determination of the frontal area of the heart and from the measurement of the depth diameter. In estimating the cardiac area of the frontal orthodiagram the source of error

lies almost entirely in completing the cardiac contour of that part of the heart shadow which merges with the aorta above and the portion of the heart which is hidden by the diaphragm below. Roesler⁹ states that the variations in completing the frontal orthodiagraphic tracing for the estimation of the cardiac area on different days by the same individual range from 2 per cent to 5 per cent, and when different individuals complete the same tracing the variations may reach 20 per cent. Table I shows cardiac area determinations on seven different frontal orthodiagrams computed on three different days by each of three individuals of varying experience. It can be seen that both experience and heart size make a slight difference. It is true that the tendency to error is less in small and vertical hearts than in hearts which are transverse in position. The reason for this is illustrated in Figs. 1 and 2, which show that the amount of the cardiac silhouette to be completed arbitrarily is considerably less in the vertical type of heart. It is safe to say from our results that with experience, no matter what the heart size may be, the individual error in completing the cardiac silhouette will be less than 5 per cent. Further, it would seem that even between different individuals the percentage variation will be, as a rule, less than 10 per cent, although on occasions it may rise as high as 12 to 15 per cent.

TABLE I

FRONTAL CARDIAC AREAS ESTIMATED FROM TRACINGS OF SEVEN DIFFERENT ORTHODIAGRAMS BY THREE INDIVIDUALS OF VARYING EXPERIENCE ON THREE DIFFERENT OCCASIONS

	FRONTAL CARDIAC AREAS							AVERAGE
	1	2	3	4	5	6	7	
A. (Experienced)	67.3 68.6 67.2	83.8 84.4 84.3	94.3 92.2 91.2	112.0 114.8 110.4	116.5 115.0 111.0	130.0 123.6 124.3	174.6 182.3 178.0	
Percentage of difference	2	1	3	4	5	5	4	3
B. (With slight experience)	70.4 69.1 70.1	85.2 85.2 87.8	97.6 97.7 97.0	115.4 110.1 110.1	117.0 115.6 117.5	123.1 137.4 130.2	184.8 173.6 180.8	
Percentage of difference	2	3	1	5	2	12	6	4
C. (With no experience)	68.0 65.4 66.7	85.0 82.5 84.4	92.3 90.8 91.3	111.2 109.8 110.8	114.3 105.2 108.3	129.9 123.0 124.3	176.1 170.6 169.6	
Percentage of difference	4	3	2	1	9	6	4	4
Percentage difference A-B	5	5	7	5	6	11	6	6
Percentage difference A-C	5	2	4	5	11	6	7	6
Percentage difference B-C	8	6	7	5	12	12	9	8

By far the most unsatisfactory measurement is that of the depth diameter, and consequently we found that the average of three separate determinations was more accurate than a single measurement. By discarding those determinations in which this measurement varied by more than 6 mm., the error was automatically limited to approximately 6 per cent for an individual volumetric determination. The ventral point for this

measurement is usually the manubrium just below its contact with the right ventricle. As a rule there is little difficulty in establishing the position of this point by fluoroscopy, although at times even the manubrium is not so clearly seen as might be expected. To locate fluoroscopically the posterior border in the lateral position, however, is frequently extremely difficult. This is particularly the case with large or transverse hearts when the retrocardiac space is obliterated, with a consequent loss of contrast. Not infrequently hilar vessel shadows, a thick chest, or obesity diminish the radiolucency of the retrocardiac space and add to the difficulties in locating the posterior cardiac border even when the heart is relatively small.

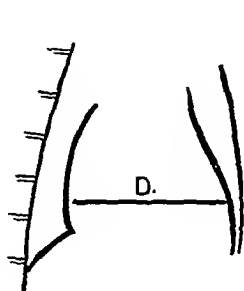


Fig. 1.

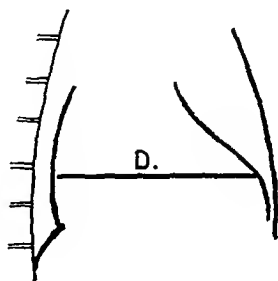


Fig. 2.

The most interesting and significant of our results are to be found in Table II. The heart volume in the same individual was determined on three successive days at approximately the same time of day (controlling the conditions by fluoroscopying the subject before breakfast made no significant difference). The percentage variations between the minimum and maximum figures for the horizontal depth diameter, the frontal cardiac area, and the heart volume can be readily seen. From the technical point of view it seems safe to say that the percentage error will be usually less than ± 10 per cent in those hearts whose volumes are 700 c.c. or less, while a percentage error of ± 10 per cent to ± 20 per cent may result in those hearts whose volume is greater than 700 c.c. In other words, the maximum technical error for normal hearts will be, in general, ± 10 per cent, while for diseased hearts with enlargement of any degree the percentage error varies considerably and may be as high as ± 20 per cent.

TABLE II
CARDIAC VOLUMETRIC DETERMINATIONS MADE BY ONE OBSERVER ON THREE SUCCESSIVE DAYS IN SEVENTEEN INDIVIDUALS

CASE NO.	D ₁	D ₂	D ₃	% DIFF.	A ₁	A ₂	A ₃	% DIFF.	V ₁	V ₂	V ₃	% DIFF.
51	7.5	7.1	7.4	6	64.5	66.8	67.3	4	305	299	314	5
216	7.8	7.5	7.0	11	79.0	79.4	78.2	2	388	375	345	12
54	8.5	8.3	8.5	2	86.4	84.5	80.6	7	463	442	432	7
127	8.4	8.2	8.3	2	92.9	97.8	98.2	6	491	505	513	4
184	7.9	8.2	8.1	4	89.1	95.1	91.1	7	443	491	465	11
154	8.3	8.6	8.4	4	108.6	107.2	112.5	5	568	581	595	5
152	8.7	9.4	8.7	8	106.8	105.5	108.3	3	585	625	594	7
153	8.2	8.4	8.0	5	115.7	112.9	114.5	2	598	597	577	4
132	10.5	9.6	9.6	9	98.0	97.4	93.5	5	648	589	565	15
*126	9.2	9.1	9.3	2	110.4	110.1	107.1	3	640	633	627	2
133	10.1	9.2	9.8	10	100.0	105.3	113.7	14	636	610	702	15
188	8.9	9.1	9.3	5	110.5	112.0	100.5	11	620	642	589	9
*193	9.3	10.6	9.7	14	129.5	122.3	114.3	13	759	817	698	17
196	10.5	9.7	9.5	11	122.0	120.2	120.0	2	807	742	749	9
198	11.0	11.1	11.4	4	119.7	126.3	123.1	6	829	883	884	7
*213	12.0	11.6	11.2	7	158.1	154.5	147.2	7	1195	1139	1039	15
*183	12.5	12.1	13.0	7	204.3	207.8	232.6	13	1609	1584	1905	20

*Heart disease.

In summary, then, it can be concluded on the basis of Bollini's^{3b} figures from heart models that with the Rohrer-Kahlstorf formula the estimated volume may vary from the actual volume by extremes of -1 per cent and +16 per cent, to which may be added a maximum technical error of ± 10 per cent in clinical application if the heart volume is less than 700 c.e. The total extremes, then, in normal hearts of less than 700 c.e. would be -11 per cent and +26 per cent. From the latter figures it would seem justifiable to conclude that except for occasional instances the volume of normal hearts can generally be estimated by the Rohrer-Kahlstorf formula with a maximum error of ± 15 per cent, as originally stated by these authors. Since the variation from the actual volume in enlarged hearts, according to Bollini, varies from +4 per cent to +42 per cent, and the maximum technical error for hearts of all sizes is ± 20 per cent, it follows that the extremes of error by the Rohrer-Kahlstorf method for enlarged hearts is theoretically -16 per cent and +62 per cent. Obviously, such results make the method of questionable value when cardiac enlargement is present.

THE HEART VOLUME IN NORMAL SUBJECTS

The data concerning the normal hearts revealed several points of interest. The range of the heart volume in males was from 400 c.e. to 900 c.e. Only eleven subjects, however, had heart volumes of over 700 c.e. The latter were all heavy, stocky individuals, and the measurements on those with heart volumes over 800 c.e. might well be questioned because of the technical difficulties. In females the range of heart volume was from 300 c.e. to 550 c.e., except for five heavy individuals.

Fig. 3 shows the variations in normal heart volume and the existence of a very definite linear correlation between heart volume and body

weight and body surface area. This is in agreement with anatomical studies on heart weight and clinical studies with various cardiac measurements, in which it has been found that of the various body measurements the closest correlation exists between body weight and heart size. As Kahlstorf found, there was in our series no parallelism between body height and heart volume.

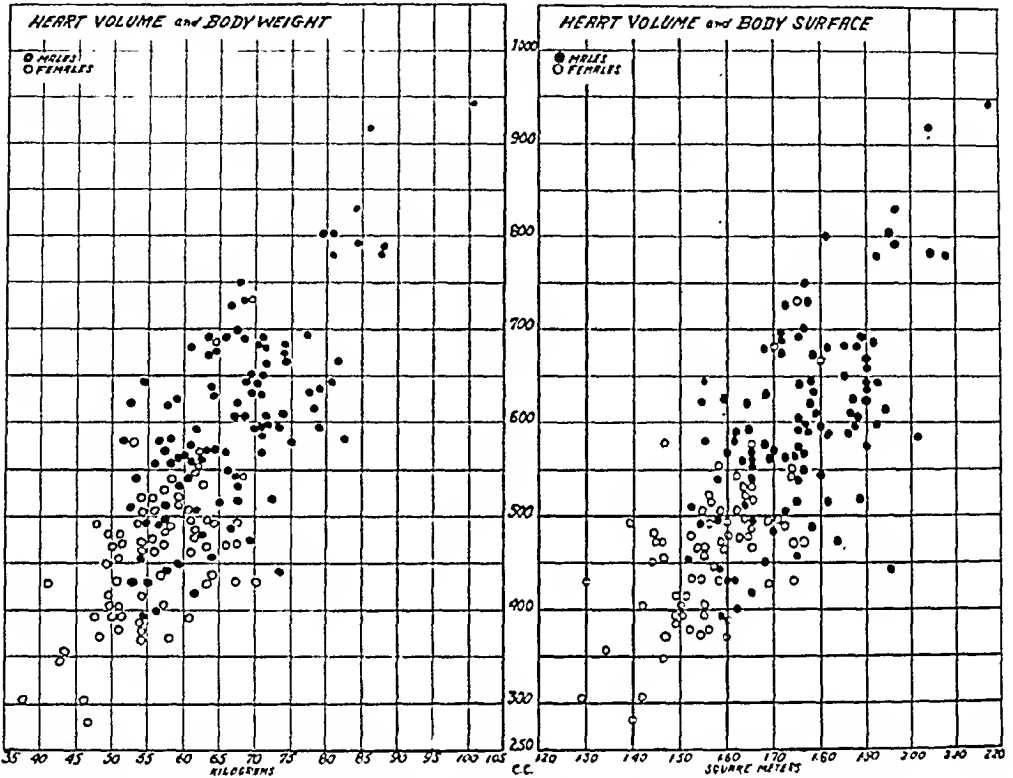


Fig. 3.—Graphs showing the correlation between heart volume and body weight and body surface area in 170 individuals with normal hearts.

Unfortunately, the body-weight, heart-volume correlation is not sufficiently close to warrant its use as a criterion for establishing normal values. From the graphs it can be seen that two individuals of the same weight may have heart volumes which vary by as much as 200 c.c. It is clear that the smaller heart could enlarge rather markedly before it would fall beyond the limits of normal as established by an index based on the body-weight, heart-volume correlation.

THE HEART VOLUME IN INDIVIDUALS WITH HEART DISEASE

It is not an uncommon experience to find individuals in whom the cardiothoracic ratio or the area of the frontal cardiac silhouette is abnormal, and in whom there are slight or equivocal findings which may or may not be indicative of heart disease. If the heart is transverse in position the situation is further confused and the abnormal measurements still more difficult to interpret. This was the group which we originally hoped to be able to clarify by the heart volume estimations. It soon became evident, however, that the boundary between normal and

abnormal heart size by this method was too wide and, further, that the position of the heart in the individuals of this group was usually transverse and, as a result, the volumetric determination more liable to technical error.

In view of the large potential theoretical error in diseased hearts we concluded that little was to be gained by an exhaustive study of subjects with heart disease. The examination of diseased hearts revealed some points of interest and one positive conclusion. The largest heart was found in a case of mitral and tricuspid stenosis, in which the volume was over 3,500 c.c. The smallest abnormal heart volume (350 c.c.) was found in a patient with long-standing chronic colitis with cachexia who had electrocardiographic changes indicating myocardial disease.

TABLE III

TYPE OF HEART DISEASE	NO. OF CASES	MINIMUM VOL.	MAXIMUM VOL.
Coronary	8	614	874
Hypertensive	6	623	1543
Valvular disease			
1. Aortic regurgitation	11	633	1417
2. Mitral stenosis	5	479	1009
3. Aortic regurgitation and mitral stenosis	3	673	1510
4. Aortic stenosis	2	825	933
5. Mitral and tricuspid stenosis	1		3503
Miscellaneous	4	896	1609

As might be expected, there was a considerable variation of the heart volume in heart disease (Table III), particularly in those individuals with valvular disease and hypertensive heart disease. This is to be expected, since the heart size in individuals with valvular disease will depend upon the type, severity, and duration of the valvular lesion, while in the hypertensive group the degree of hypertension and the duration will be the important factors in determining the extent of cardiac enlargement.

TABLE IV

CARDIAC MEASUREMENTS MADE ON AN INDIVIDUAL WITH HEART DISEASE AT DIFFERENT PERIODS DURING CLINICAL IMPROVEMENT

	T	TH	CTR	D	A	V
5/27/37	17.5	26.5	66%	12.6	164	1303
7/ 9/37	16.8	26.4	64%	10.8	188	1279
8/19/37	14.8	26.4	56%	10.6	147	983
10/13/37	14.4	26.2	55%	9.6	140	852

A significant point was brought out by the study of a patient with cardiac enlargement of undetermined etiology. This patient was followed, at intervals, from the time of admission with heart failure, through convalescence, and for a period during which he was carrying on a relatively normal life. Table IV shows the gradual diminution in

heart size, which is much more strikingly shown by the heart volume estimation than by any of the other cardiac measurements. It would have been interesting to follow a series of individuals with heart failure before and after treatment. However, the opportunity to make such comparisons without discomfort and possible harm to the patient does not present itself frequently. It is clear that both the theoretical and technical errors would be relatively constant when volumetric estimations are made on the same heart, so that the major objections to the use of the formula would be largely eliminated. By the use of the volume figure in such a manner we believe that a better concept is obtained of the actual increase or decrease in heart size either during a period of heart failure or in following a patient over a period of years.

SUMMARY AND CONCLUSIONS

1. The heart volume (in cubic centimeters) as estimated by the Rohrer-Kahlstorf formula (area in square centimeters of the heart shadow in the frontal silhouette times depth in centimeters in the lateral silhouette times 0.63, a constant) was determined in 100 adult males and seventy adult females with clinically normal hearts. The heart volume was also estimated in forty individuals with the more common cardiac abnormalities.

2. The theoretical basis for the formula is discussed and its clinical application is described.

3. The percentage of error in the practical application of the Rohrer-Kahlstorf formula is estimated by combining the inherent error in the formula as determined by Bollini (through comparison of the computed heart volume by formula, with the actual heart volume of heart models by water displacement) and the maximum technical error as determined by our results. In normal hearts the error varies from -11 per cent to +26 per cent, so that with only a few exceptions the maximum error will be within ± 15 per cent, as originally stated by both Rohrer and Kahlstorf. In enlarged hearts the error varies widely from -16 per cent to +62 per cent, so that the method cannot be applied with any degree of accuracy in many instances of cardiac enlargement.

4. The volume of normal hearts ranged from 400 c.c. to 900 c.c. in males, and from 300 c.c. to 550 c.c. in females. Only eleven males, however, had heart volumes over 700 c.c., and those over 800 c.c. may well be questioned because of technical difficulties. A linear correlation was found to exist between heart volume and body weight and body surface. This correlation, however, was not sufficiently close to allow the derivation of a reliable index as a criterion for normal, inasmuch as the normal range was from 6 c.c. to 12 c.c. per kilogram of body weight and from 200 c.c. to 450 c.c. per square meter of body surface (males 6.7 to 11.8 c.c. per kilogram, and 250 to 450 c.c. per square meter; females 6.1 to 10.6 c.c. per kilogram and 200 to 435 c.c. per square meter). No parallelism was found between body height and heart volume.

5. The diseased hearts showed a wide range of heart volumes. The largest was 3,500 c.e. in a case of mitral and tricuspid stenosis, the smallest 350 c.e. in a case of cachexia due to chronic colitis in which the electrocardiogram showed evidence of coronary insufficiency or myocardial disease. The changes in heart volume were followed in one case through a period of heart failure and during convalescence. Since the percentage of error would be relatively constant when determinations are made on the same heart, and since the volumetric figure gives a better concept of actual heart size, it is believed that there is a definite advantage in using volumetric estimations to follow the changes in the size of the heart in individual patients through a period of heart failure or over a period of years.

6. In general we must conclude that the volumetric estimation of heart size is no more reliable by itself than are other heart measurements. It is true of volumetric determinations as of heart measurements of any kind that, due to their wide normal variation, they must be interpreted in relation to the impression arrived at during fluoroscopy and, particularly when measurements are questionable, in relation to the expected normal position (vertical or transverse) and shape of the heart in the thorax. It should be recognized that the position of the heart and its normal size and shape depend largely upon body build and occasionally upon an abnormality of the thoracic cage itself; it is always important to consider these factors in the interpretation of heart size and measurements. Further study of the correlation of heart size and shape with various anthropometric measurements other than weight, height, and body surface may yield formulas more reliable and useful than exist at present. We are contemplating the pursuit of such a study.

Addendum: The paper by Liljestrand, Lysholm, Nylin, and Zachrisson, to appear in the *AMERICAN HEART JOURNAL*, entitled "The Normal Heart Volume in Man," confirms the conclusions noted by us concerning the present unsatisfactory basis for the determination of normal heart volume. They found, as we did, a wide variation of the normal, 7.0 to 13.0 c.e. of heart volume per kilogram of body weight and between 250 and 490 c.e. per square meter of body surface, in 101 healthy men whose ages ranged from 21 to 47 years.

REFERENCES

1. Palmieri, G.: Ueber meine Methode der plastischen Darstellung des Herzens am Lebenden (Radioplastik), *Acta radiol.* 10: 127, 1929.
2. Bardeen, C. R.: Estimation of Cardiac Volume by Roentgenology, *Am. J. Roentgenol.* 9: 823, 1922.
3. Bollini, V.: Note di cardiolumetria sperimentale.
 - (a) I. Le dimensioni ortocardiografiche in rapporto all'orientamento del cuore, *Radiol. e Fisic. Med.* 2: 193, 1935.
 - (b) II. La formula di calcolo del "valore cardiaco," *Radiol. e Fisic. Med.* 2: 358, 1935.

4. Kahlstorf, A.: Ueber eine orthodiagraphische Herzvolumenbestimmung, Fortschr. a. d. Geb. d. Röntgenstrahlen 45: 123, 1932.
5. Rohrer, F.: Volumbestimmung von Koerperhoehlen und Organen auf orthodiagraphischem Wege, Fortschr. a. d. Geb. d. Röntgenstrahlen 24: 285, 1916-17.
6. Sallotti, A.: Il volume del cuore ai raggi, X Atti Soc. Med. Chir. Padova, March 27, 1927.
7. Benedetti, P.: L'évaluation métrique individuelle du coeur (méthode tridimensionnelle), Arch. d. mal. du coeur 28: 283, 1935.
8. Benedetti, P., and Bollini, V.: Valutazione metrica e ispettiva del cuore dei cardiopazienti, Arch. di pat. e clin. med. 15: 131, 1935; 15: 303, 1935; 16: 85, 1936.
9. Roesler, H.: Clinical Roentgenology of the Cardiovascular System, p. 62, Baltimore, 1937, Charles C. Thomas.

THE EFFECTS OF ALKALOSIS AND OF ACIDOSIS UPON THE HUMAN ELECTROCARDIOGRAM*†

PAUL S. BARKER, M.D., ANN ARBOR, MICH., E. LEE SHRADER, M.D.,
AND ETHEL RONZONI, PH.D., ST. LOUIS, MO.

MUCH attention has been given to electrocardiographic changes caused by heart disease or by drugs used in the treatment of heart disease. Little notice has been taken of transient changes not related to heart disease. It has long been known that such changes may be caused by exercise,¹ drinking ice water,² stimulation of the vagus or sympathetic nerves,^{1, 3, 4} and by alterations in the position of the heart such as may be produced by respiration or changes in posture.^{1, 5}

There have been a few observations upon the effects of alkalosis and of acidosis upon the electrocardiogram. In 1926, Schott⁶ reported that in dogs the T-waves may be made taller by giving hydrochloric acid intravenously, and smaller by giving sodium carbonate intravenously. Transient reduction in the amplitude of T in man during the tetany of spontaneous overbreathing was reported in 1929 by Kronenberger and Ruffin,⁷ and in 1932 by McCance.⁸ Simpson⁹ has observed reduction in the amplitude of T in patients undergoing artificial fever therapy, all of whom had alkalosis.

An increase in the duration of electrical systole (the Q-T interval) in man has been observed by Bazett¹⁰ following exercise, and by Carter and Andrus¹¹ in alkalosis. Samojloff³ and Bazett noted an increase in the duration of systole after giving atropine. In various conditions in which the blood serum calcium is reduced the duration of electrical systole is increased,¹¹⁻¹⁴ while an elevation of serum calcium may be accompanied by a reduction in the duration of electrical systole.^{12, 13, 15}

The present study was prompted by the observation of T-wave changes occurring during an episode of hysterical overventilation with tetany.

CASE REPORT

The patient was a 23-year-old male medical student who was conscious of his heart beat, but who showed on physical and electrocardiographic examination on May 16, 1923, no evidence of cardiac abnormality (Fig. 1 A). On Dec. 20, 1923, he was admitted to the hospital complaining of difficult breathing and cramping pains in the abdomen and extremities. Examination showed deep and rapid breathing and the typical carpopedal spasm of tetany, but revealed no abnormality of the heart or lungs. An electrocardiogram, however, showed pronounced flattening of the

*From the Departments of Internal Medicine of the Medical Schools of Washington University and of the University of Michigan.

†Presented in part before the Central Society for Clinical Research Nov. 1, 1935, Chicago. A brief preliminary report appeared in the University Hospital Bulletin, 1: 50, 1935.

Received for publication Aug. 12, 1938.

T-waves (Fig. 1 *B*). When the patient was reassured and persuaded to breathe normally his symptoms rapidly disappeared, and on the following day his electrocardiogram was normal (Fig. 1 *C*), resembling that of May 16.

Although it was thought that the patient had hysterical overventilation, the question remained as to whether he might have had a transient cardiac condition which caused the dyspnea and the T-wave changes, or whether overventilation was responsible for the changes in the electrocardiogram.

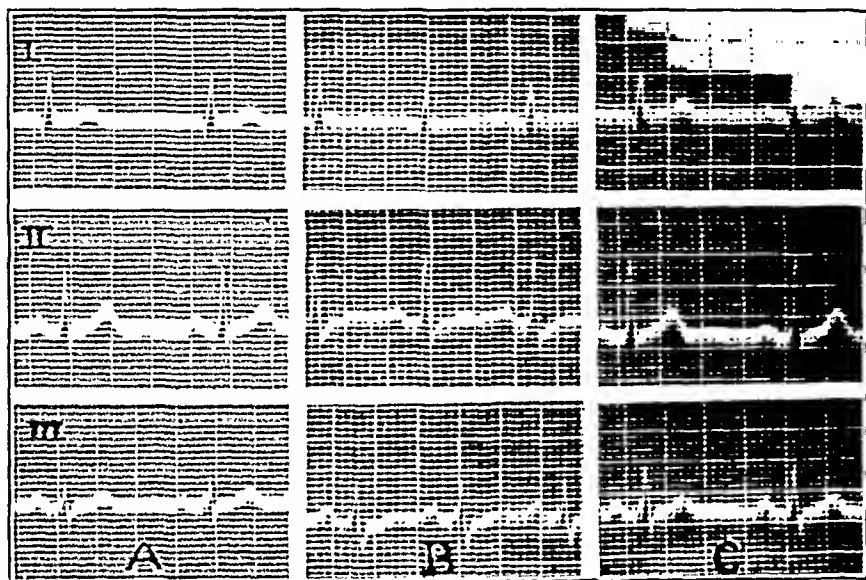


Fig. 1.—Electrocardiograms of patient. *A*, May 16, 1923. *B*, Dec. 20, 1923, during hysterical overventilation. *C*, Dec. 21, 1923.

EXPERIMENTAL OBSERVATIONS

In this study seven normal young adults served as subjects for forty experiments. The experiments included voluntary overventilation, voluntary overventilation with a large dead space, the ingestion of large amounts of sodium bicarbonate, exercise, exercise after the ingestion of sodium bicarbonate, ingestion of large amounts of ammonium chloride, and rebreathing. The effects of these procedures upon the electrocardiogram and upon the hydrogen-ion concentration, lactic acid content, and carbon-dioxide combining power of blood from the veins of the arms were investigated. In some instances the serum calcium and phosphorus were determined. Electrocardiograms and samples of venous blood were taken before and at suitable intervals following the above procedures and, when possible, as in overventilation, during the procedure.

In determining the amplitudes of the various electrocardiographic deflections, the measurements in ten successive beats were averaged and care was taken to avoid errors which might result from the effects of respiratory movements upon the curves. The standardization of each curve was recorded, and corrections were made for errors in standardization. These, however, were never great.

Overventilation.—Four subjects served for thirteen experiments in voluntary overbreathing to the point of well-developed tetany.¹⁶ The tetany usually developed within five minutes, in one subject in three minutes, but in most of the experiments overbreathing was performed for eight to sixteen minutes, and in one instance twenty-four minutes. In all of these experiments the T-waves of Lead I became much smaller during the overbreathing, and in ten instances T of Lead II became smaller (Figs. 2, 3, and 4). In two instances T of Leads II and III became slightly taller, while in five other experiments T of Lead III became taller. In nearly all of the experiments the R-waves became smaller in Lead I and taller in Lead III. In three experiments, however, the R-waves became smaller in Lead III, and in two of these the T-waves of Lead III became taller (Table I).

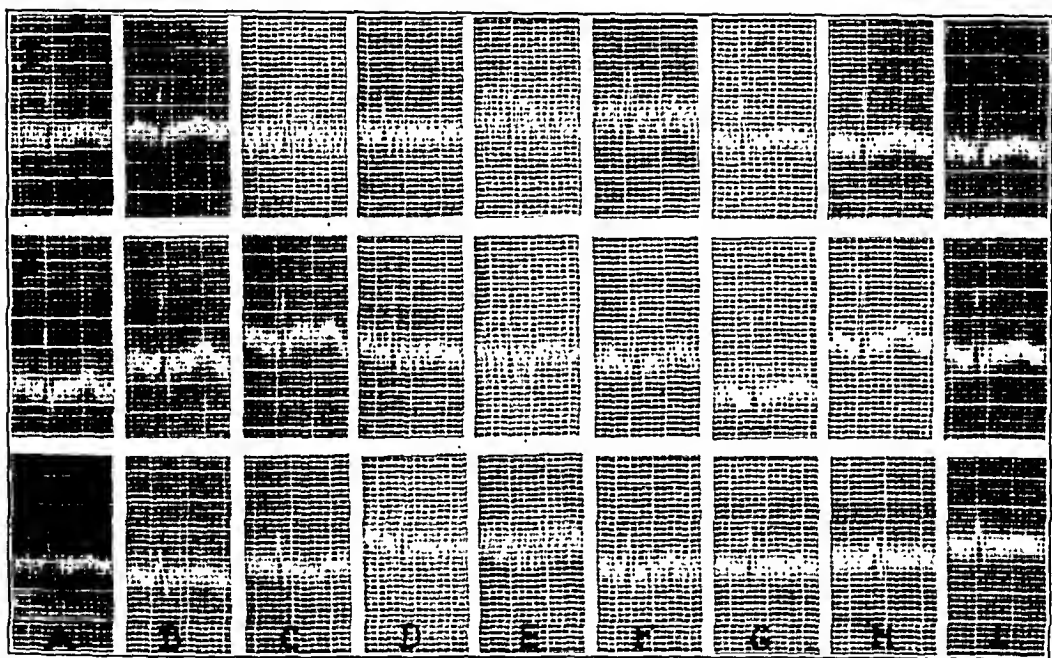


Fig. 2.—Experiment 23, subject A, voluntary overventilation for twenty-four minutes. A, control. B and C, during overventilation. D, one minute and E, three minutes after cessation of overventilation. F, G, and H, and I at approximately ten-minute intervals. The curves show the effects of contraction of the voluntary muscles due to tetany.

In all of these experiments tetany was produced, but in only ten experiments were blood samples taken. These showed alkalosis. The hydrogen-ion concentration of the blood from the arm veins changed from values of 7.31 to 7.38 in the control specimens to values of 7.46 to 7.65 in samples taken at the height of the tetany, or just before the overventilation was terminated. The hydrogen-ion concentration returned to normal within two to five minutes after the overbreathing was stopped. The electrocardiographic changes seemed to be related more closely to the elevation of the hydrogen-ion concentration than to other changes in

TABLE I
THE EFFECTS OF VOLUNTARY OVERVENTILATION UPON T AND R OF THE ELECTROCARDIOGRAM*

EXP. NO.	SUBJECT	BLOOD PH	T-WAVES (MILLIVOLTS)			R-WAVES (MILLIVOLTS)		
			LEAD I	LEAD II	LEAD III	LEAD I	LEAD II	LEAD III
1	C	7.38 to 7.53	0.30 to 0.16 smaller	0.17 to -0.06 smaller	-0.17 to -0.22 smaller	1.40 to 0.95 smaller	1.32 to 2.14 taller	0.95 to 1.78 taller
2	D	7.36 to 7.52	0.32 to 0.19 smaller	0.38 to 0.33 smaller	0.07 to 0.14 taller	1.25 to 0.75 smaller	1.55 to 1.59 no change	0.29 to 0.50 taller
7	B		0.28 to 0.15 smaller	0.26 to 0.09 smaller	0.04 to -0.08 smaller	1.36 to 1.06 smaller	2.68 to 2.68 no change	1.59 to 2.18 taller
8	B		0.34 to 0.17 smaller	0.37 to 0.31 smaller	0.08 to 0.14 taller	1.28 to 0.99 smaller	2.19 to 2.16 no change	1.30 to 1.59 taller
9	B	7.32 to 7.50	0.31 to 0.19 smaller	0.32 to 0.12 smaller	0.05 to -0.05 smaller	0.95 to 0.77 smaller	2.22 to 1.78 smaller	1.36 to 1.86 taller
10	B	7.31 to 7.52	0.18 to 0.14 smaller	0.16 to 0.06 smaller	0.01 to -0.01 smaller	0.73 to 0.72 no change	2.05 to 1.65 smaller	1.40 to 1.77 taller
11	B	7.32 to 7.46	0.29 to 0.15 smaller	0.37 to 0.37 no change	0.08 to 0.17 taller	0.83 to 0.70 smaller	1.95 to 2.03 taller	1.12 to 1.00 smaller
20	A		0.24 to 0.04 smaller	0.16 to 0.19 taller	-0.02 to 0.09 taller	1.16 to 0.67 smaller	1.14 to 1.31 taller	0.48 to 1.07 taller
21	A	7.35 to 7.55	0.21 to 0.06 smaller	0.14 to 0.13 smaller	-0.05 to 0.05 taller	1.05 to 0.40 smaller	1.35 to 1.20 smaller	0.75 to 0.90 taller
22	A	7.31 to 7.58	0.13 to -0.01 smaller	0.06 to -0.02 smaller	-0.09 to 0.01 taller	0.52 to 0.22 smaller	1.15 to 0.72 smaller	0.78 to 0.64 smaller
23	A	7.35 to 7.65	0.10 to 0.01 smaller	0.20 to 0.00 smaller	0.08 to -0.03 smaller	0.63 to 0.59 smaller	0.93 to 0.93 no change	0.39 to 0.55 taller
24	A	7.36 to 7.55	0.11 to 0.02 smaller	0.09 to 0.09 smaller	0.00 to 0.00 smaller	0.88 to 0.32 smaller	1.26 to 0.76 smaller	0.72 to 0.55 smaller
25	A	7.35 to 7.55	0.09 to 0.00 smaller	0.09 to 0.09 taller	0.03 to 0.08 taller	0.91 to 0.71 smaller	1.19 to 1.25 no change	0.64 to 0.95 taller

*The changes in the pH of the blood, from the control to the height of the alkalosis, are shown. The figures for T and R indicate the changes from the control values to those at the height of the alkalosis. The general trend of the changes in these waves is also indicated. The data given in Tables II and III are presented similarly.

the venous blood, such as carbon-dioxide combining power, carbon-dioxide content, lactic acid content, or serum calcium or phosphorus content. There was not, however, a strict parallelism between the changes in the electrocardiograms and the changes in the hydrogen-ion concentration of the blood (Figs. 2 and 4).

In some of the experiments the electrocardiographic changes were of the type which might be caused by a change in the position of the heart, such as might occur if the diaphragm should be depressed and the heart should assume a more vertical position, causing a shift of its long axis to the right.⁵ It is possible that a slight, transient emphysema of the lungs may have occurred, and that this may have been accompanied by a slight change in the position of the heart. The changes in the electrocardiograms are not, however, attributed to this alone, for the following reasons. In the first place, overventilation produced no changes in the position of the heart or diaphragm which were apparent upon physical examination. Secondly, in some of the experiments the T-wave changes were not accompanied by similar changes in the R-waves. Lastly, the observations to be described presently make such an explanation unlikely.

Voluntary overventilation removes carbon dioxide from the body in abnormally large amounts, and in this manner causes alkalosis. If, however, the atmosphere breathed is sufficiently rich in carbon dioxide, excessive removal of the gas will not occur, and alkalosis will not develop. Two subjects served for three experiments in which they voluntarily overbreathed through a large tube into a large bottle, the wide neck of which was open to the air of the room. This had the effect of increasing the dead space by about nine liters, without causing any appreciable resistance to breathing. The rate, depth, and duration (thirteen to fourteen minutes) of the overbreathing were approximately the same as in the experiments in which tetany developed. With the large dead space, however, the carbon-dioxide content of the air breathed soon reached a sufficient concentration to prevent the development of alkalosis. Samples of venous blood taken near the end of the period of overbreathing showed no change in the hydrogen-ion concentration in two experiments, and a slight change toward the acid side in one experiment, as compared with the controls. Samples of air from the dead space, taken just before the termination of overbreathing, showed carbon dioxide values of 4.8, 6.1, and 5.0 volumes per cent, and oxygen values of 18.5, 16.0, and 18.4 volumes per cent, respectively, for the three experiments. It is unfortunate that venous blood was not taken during the first few minutes of overbreathing, as it is possible that a slight degree of alkalosis may have developed at first, before the carbon dioxide of the air breathed had increased sufficiently to prevent it. One subject recognized, during the first few minutes, the tingling of the extremities which always preceded the appearance of tetany.

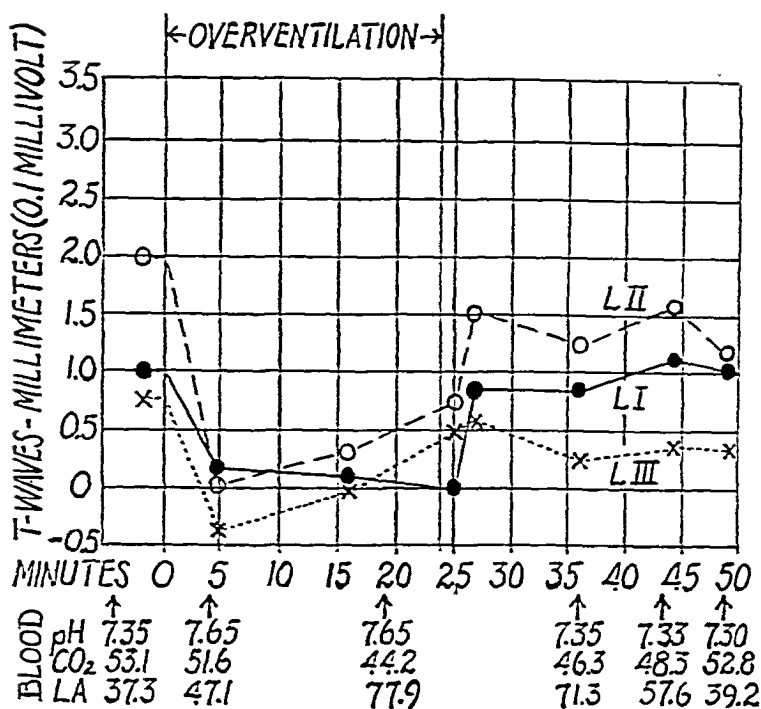


Fig. 3.—Experiment 23, subject A, showing the relation of the electrocardiographic changes to changes in the venous blood. In this and subsequent figures Lead I is represented by dots, Lead II by circles, and Lead III by crosses, while CO₂ refers to the carbon-dioxide combining power and LA to the lactic acid content of venous blood.

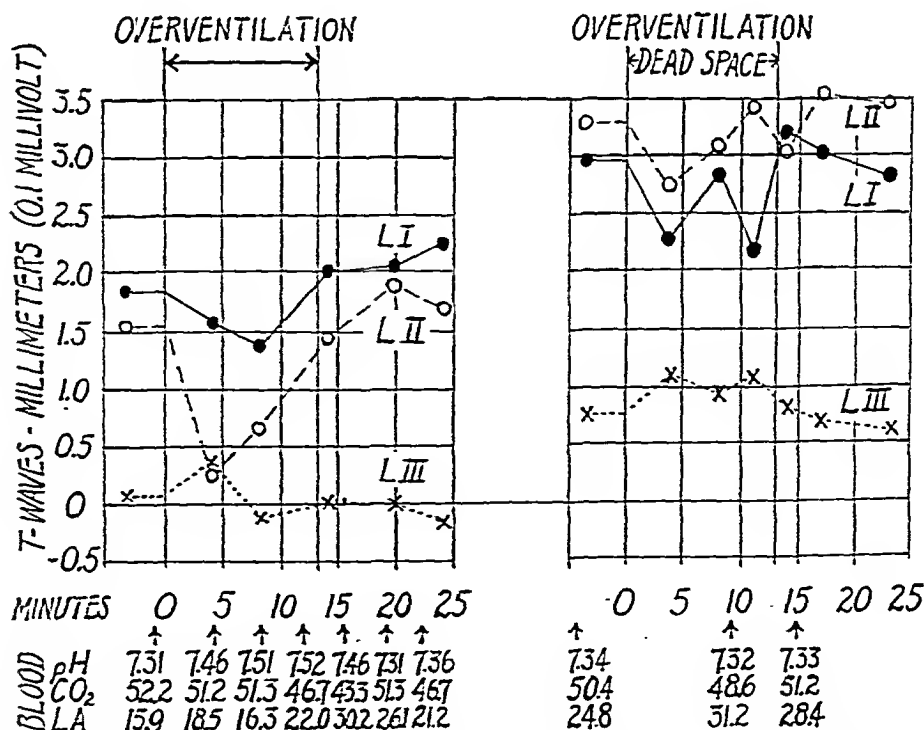


Fig. 4.—Experiment 10, subject B, voluntary overventilation, and experiment 12, subject B, voluntary overventilation with a large dead space.

The electrocardiograms showed slight changes (Figs. 3, 4, and 5). In all, the T-waves became smaller in the first few minutes of the overbreathing, only to become taller a few minutes later. In the experiment (Fig. 5) in which the reduction in amplitude of T appeared most pronounced, the T-waves of the control curve were unusually tall for this subject. The R-waves showed but slight changes, usually but not always in the same direction as the T-wave changes. In none of these experiments were the changes as pronounced or the T-waves as flattened as in the experiments in which alkalosis and tetany were produced (compare Figs. 2 and 5).

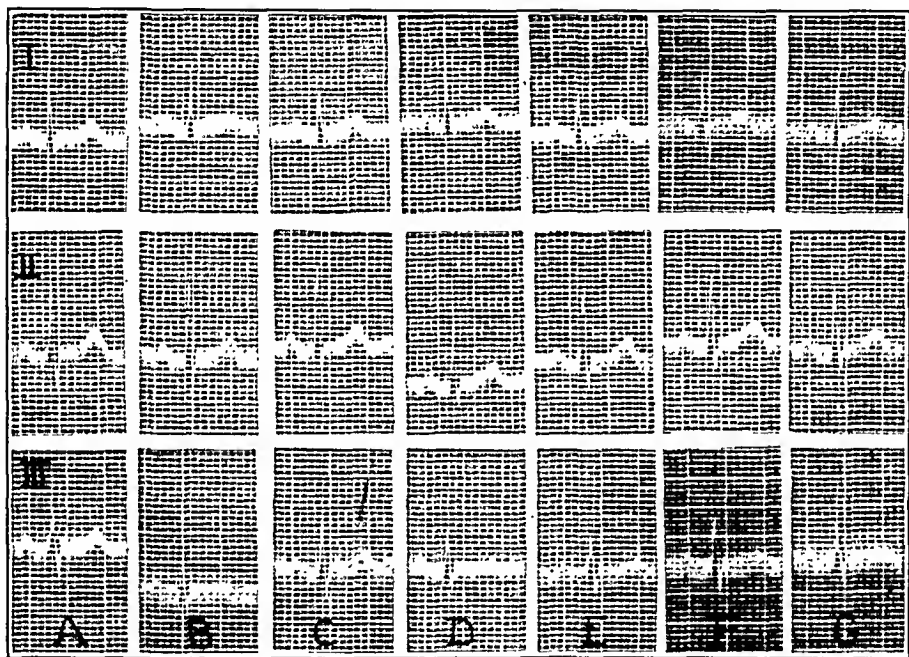


Fig. 5.—Experiment 26, subject A, voluntary overventilation with a large dead space, in which the pH and CO_2 combining power of venous blood showed no significant change. A, control. B, C, and D during overventilation. E, F, and G at approximately four-minute intervals following the cessation of overventilation. Compare with Fig. 2.

Sodium Bicarbonate.—In order to investigate further the question whether the electrocardiographic changes observed were related to alkalosis or to the excessive respiratory movements, four subjects served for seven experiments in which sodium bicarbonate was given by mouth in single doses of 25 to 50 gm. Moderate alkalosis was produced in all seven experiments, the hydrogen-ion concentration of the venous blood rising from values of 7.32 to 7.33 in the controls, to values of 7.48 to 7.58 at the height of the alkalosis. The carbon-dioxide combining power changed from control levels of 49.5 to 53.2 volumes per cent, to 64.6 to 74.8 volumes per cent at the height of the alkalosis. In none of these experiments did tetany occur. The hydrogen-ion concentration and carbon-dioxide combining power reached their highest values within

TABLE II
THE EFFECTS OF SODIUM BICARBONATE UPON T AND R OF THE ELECTROCARDIOGRAM

EXP. NO.	SUBJECT	BLOOD PH	T-WAVES (MILLIVOLTS)			R-WAVES (MILLIVOLTS)		
			LEAD I	LEAD II	LEAD III	LEAD I	LEAD II	LEAD III
3	E	7.33 to 7.48	0.13 to 0.15 taller	0.08 to 0.16 taller	0.00 to 0.01 taller	1.08 to 1.06 no change	1.16 to 1.32 no change	0.35 to 0.30 no change
4	F	7.33 to 7.53	0.20 to 0.13 smaller	0.25 to 0.15 smaller	0.10 to 0.11 taller	1.22 to 1.10 no change	1.35 to 1.19 no change	0.60 to 0.40 no change
14	B	7.32 to 7.52	0.21 to 0.24 no change	0.15 to 0.19 no change	-0.10 to -0.07 no change	1.14 to 1.47 taller	1.92 to 1.81 no change	1.02 to 0.65 smaller
27	A		0.08 to 0.06 smaller	0.15 to 0.09 smaller	0.06 to 0.02 smaller	0.68 to 0.48 smaller	1.16 to 1.12 no change	0.40 to 0.65 taller
28	A	7.33 to 7.58	0.17 to 0.02 smaller	0.31 to 0.08 smaller	0.12 to 0.02 smaller	0.55 to 0.85 taller	0.94 to 0.80 no change	0.41 to 0.14 smaller
15*	B		0.27 to 0.13 smaller	0.27 to 0.20 smaller	0.02 to 0.06 taller	1.06 to 1.17 taller	1.76 to 1.64 no change	0.88 to 0.41 smaller
29*	A	7.34 to 7.58	0.14 to 0.13 smaller	0.19 to 0.22 smaller	0.08 to 0.08 smaller	0.83 to 0.55 no change	1.02 to 1.04 no change	0.42 to 0.37 no change

*Control observations not made; the figures for the controls are the averages of many control observations.

one to three hours after the ingestion of the sodium bicarbonate, and these values often persisted for five to nine hours. The electrocardiographic changes were usually apparent within two or three hours, and were most pronounced five or six hours after the ingestion of the sodium bicarbonate (Figs. 6 and 7).

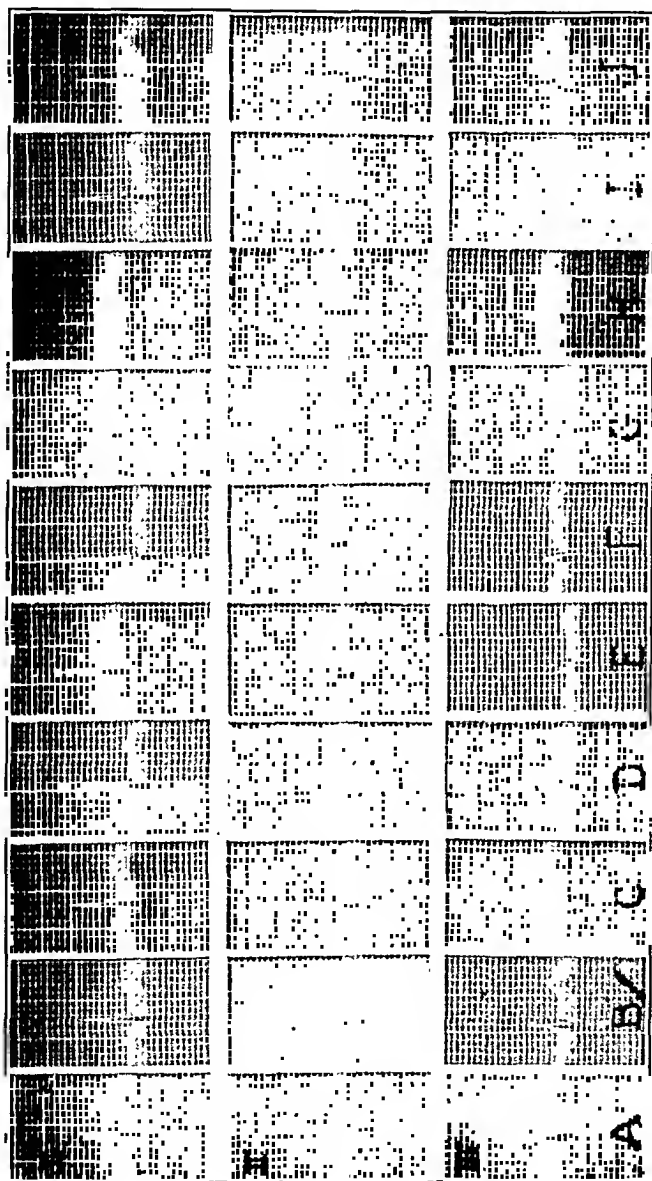


Fig. 6.—Experiment 28, subject A. A, control. B to J, curves taken at hourly intervals following the ingestion of 50 gm. of sodium bicarbonate. J, twenty-six hours later. The pH of the venous blood rose to 7.58, and the CO_2 combining power to 74.8 vol. per cent (see Fig. 7).

In five of the seven experiments with sodium bicarbonate, the alkalosis was accompanied by a definite reduction in the amplitude of the T-waves of the electrocardiograms in Leads I and II or in all three leads (Table II). In one of the experiments there were no significant changes in the T-waves, while in one experiment the T-waves became slightly taller. The R-waves usually showed no significant changes, and when they

became slightly taller or slightly smaller, these changes did not appear to be related to the T-wave changes.

The alkalosis produced by sodium bicarbonate was accompanied by a reduction in the amplitude of the T-waves. The electrocardiographic changes, however, were not directly proportional to the degree of alkalosis; the relationship was qualitative, not quantitative. This was true for both hydrogen-ion concentration and carbon-dioxide combining power.

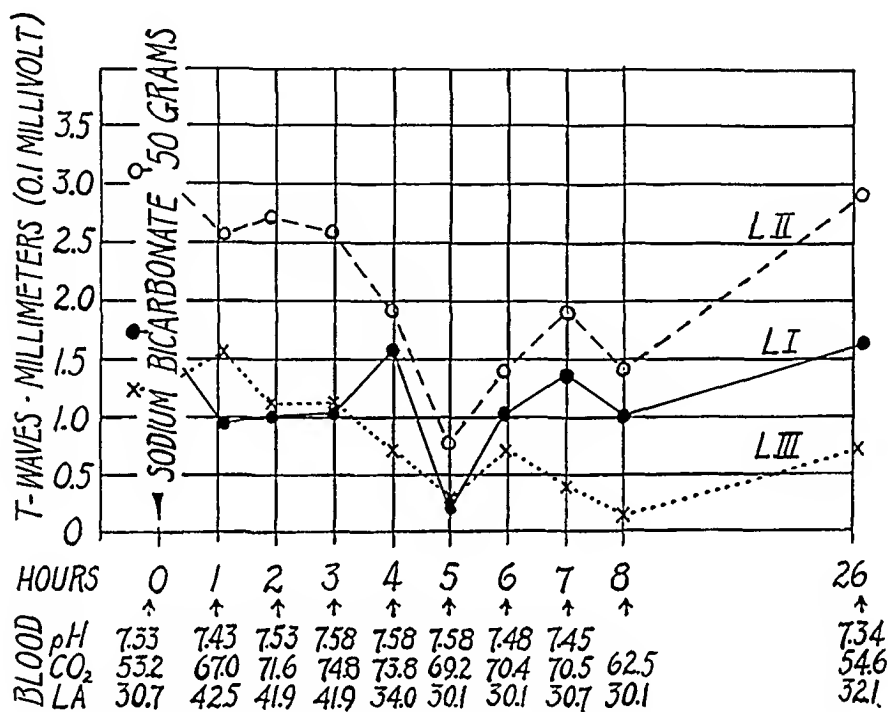


Fig. 7.—Experiment 28, subject A. Changes in the T-waves following the ingestion of 50 gm. of sodium bicarbonate.

Exercise.—Four subjects were used for one experiment each. The exercise consisted in running up and down stairs until shortness of breath and fatigue were quite pronounced. This required two and one-half to four minutes. The work performed, as estimated from the weight of the subject and the height through which he raised his weight, was 2400 to 4000 kilogram-meters. Definite acidosis was produced. The hydrogen-ion concentration of the venous blood fell to between 7.12 and 7.18, and returned to approximately normal within fifteen to thirty minutes. The carbon-dioxide combining power and lactic acid content returned to normal more gradually in about one hour, as had been observed by Barr, Himwich, and Green.^{17, 18}

In the electrocardiograms the T-waves became much taller immediately after the exercise (Figs. 8 and 9), taller in all three leads in three experiments, and in Leads I and II in the other (Table III). In this last experiment T was inverted in Lead III, and became more deeply inverted after exercise. The T-waves returned to approximately normal

TABLE III
THE EFFECTS OF ACIDOSIS UPON T AND R OF THE ELECTROCARDIOGRAM

EXP. NO.	SUBJECT	BLOOD PH	T-WAVES (MILLIVOLTS)			R-WAVES (MILLIVOLTS)		
			LEAD I	LEAD II	LEAD III	LEAD I	LEAD II	LEAD III
5	F	7.33 to 7.18	0.14 to 0.17 taller	0.22 to 0.32 taller	0.09 to 0.13 taller	0.78 to 0.78 taller	0.95 to 1.22 taller	0.20 to 0.31 taller
6	G	7.30 to 7.15	0.16 to 0.20 taller	0.09 to 0.10 taller	-0.08 to -0.10 deeper	0.80 to 0.81 taller	0.45 to 0.48 taller	-0.38 to -0.32 S less deep
16	B		0.20 to 0.32 taller	0.11 to 0.54 taller	-0.07 to +0.23 taller	0.78 to 0.63 smaller	1.92 to 2.28 taller	1.25 to 1.74 taller
30	A	7.33 to 7.12	0.17 to 0.19 taller	0.15 to 0.28 taller	0.06 to 0.11 taller	0.80 to 0.66 smaller	1.35 to 1.15 smaller	0.86 to 1.22 taller
4*	F	7.53 to 7.18	0.13 to 0.26 taller	0.15 to 0.48 taller	0.11 to 0.29 taller	1.10 to 1.12 no change	1.18 to 1.18 no change	0.39 to 0.70 taller
15*	B		0.13 to 0.31 taller	0.20 to 0.67 taller	0.06 to 0.31 taller	1.17 to 0.88 smaller	1.64 to 2.16 taller	0.41 to 1.11 taller
29*	A	7.58 to 7.30	0.13 to 0.27 taller	0.23 to 0.43 taller	0.08 to 0.16 taller	0.56 to 0.37 smaller	1.04 to 0.71 smaller	0.37 to 0.58 taller
17†	B	7.33 to 7.27	0.27 to 0.27 no change	0.27 to 0.31 taller	0.02 to 0.11 taller	1.06 to 1.31 taller	1.76 to 2.48 taller	0.88 to 1.64 taller
18	B	7.33 to 7.30	0.28 to 0.30 taller	0.26 to 0.39 taller	0.03 to 0.07 taller	1.22 to 1.17 taller	2.13 to 2.42 taller	1.10 to 1.56 taller
31†	A	7.34 to 7.26	0.14 to 0.18 taller	0.20 to 0.31 taller	0.08 to 0.11 taller	0.83 to 0.66 smaller	1.02 to 1.04 no change	0.42 to 0.41 no change
35	A		0.12 to 0.14 taller	0.30 to 0.33 taller	0.15 to 0.20 taller	0.37 to 0.19 smaller	0.85 to 0.96 taller	0.55 to 0.77 taller

*In these experiments the exercise was undertaken during alkalosis produced by sodium bicarbonate (see text and Table II).

†Control observations not made; the figures for the controls are the averages of many control observations.

within five to ten minutes after the exercise, and in two experiments they were slightly smaller than normal from ten to fifteen minutes after the exercise, while the venous blood still showed evidence of acidosis.

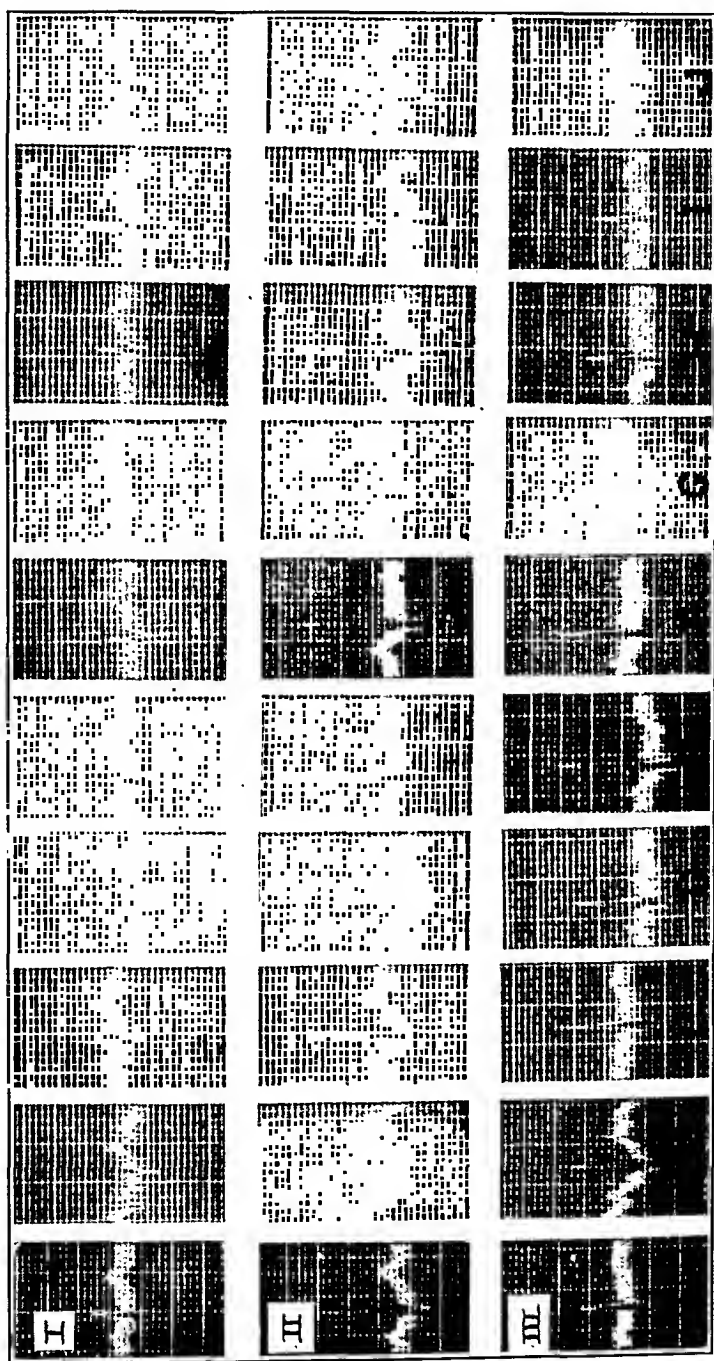


Fig. 8.—Experiment 30, subject A. A, control. B to J, following exercise in which approximately 4000 kilogram-meters of work were performed in four minutes (see Fig. 9).

The R-waves changed but little. They became slightly taller in Leads II and III, and in one experiment slightly smaller in Lead I. The heart rate did not return to normal for twenty to thirty minutes after the exercise.

Exercise is followed by acidosis and by a striking increase in the amplitude of the T-waves. In these experiments, also, the electro-

cardiographic changes were not directly proportional to the degree of acidosis, whether estimated by the hydrogen-ion concentration or by the carbon-dioxide combining power. The relationship was qualitative, not quantitative.

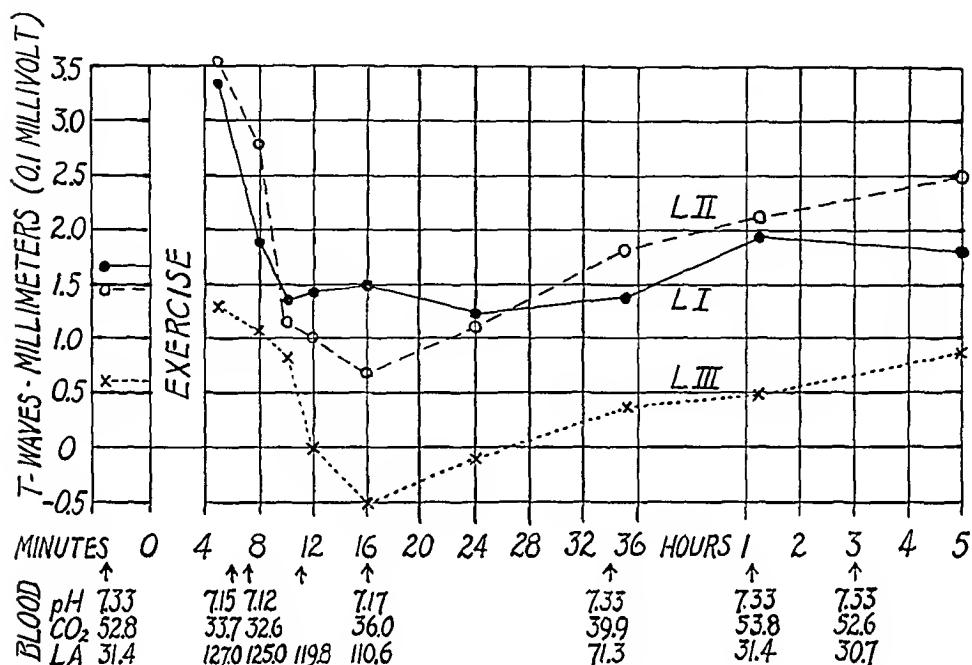


Fig. 9.—Experiment 30, subject A. T-wave changes following strenuous muscular exercise.

In three of the experiments in which sodium bicarbonate was administered the subjects exercised exactly as in the experiments just described. The exercise was performed one and one-third, three and one-fourth, and four hours, respectively, after the ingestion of the sodium bicarbonate. Alkalosis was well developed at the time of the exercise, and in two of the experiments the T-waves had become smaller. In all three experiments the T-waves of all three leads became much taller after exercise, reaching values slightly higher than after exercise alone. The R-waves did not change significantly (Table III). The hydrogen-ion concentration and carbon-dioxide combining power of the venous blood, which had shown alkalosis just before the exercise, revealed mild acidosis following the exercise. Within thirty to forty-five minutes, however, the alkalosis had returned to almost the same degree as before the exercise.

It is interesting to note that the electrocardiographic changes were not directly proportional to the degree of acidosis. Indeed, in one experiment (Exp. 29) the hydrogen-ion concentration and carbon-dioxide combining power had reached 7.58 and 74.8 volumes per cent, respectively, four hours after the ingestion of 50 gm. of sodium bicarbonate. At this point the exercise was performed and the hydrogen-ion concentration and carbon-dioxide combining power fell to only 7.30 and 36.8 volumes

per cent, respectively. In another experiment (Exp. 4), eighty minutes after the ingestion of 25 gm. of sodium bicarbonate the hydrogen-ion concentration and carbon-dioxide combining power had reached 7.53 and 74.2, respectively. At this point exercise reduced them to 7.18 and 44.3, respectively. The changes in the T-waves, however, were more pronounced in the former than in the latter experiment.

It was observed that exercise after sodium bicarbonate was followed by shortness of breath and fatigue of about the same degree as following exercise alone. Indeed, there was very little difference in these symptoms when the pH was 7.30 following exercise after sodium bicarbonate, and when the pH was 7.12 following exercise alone. In other experiments the rate and volume of respiration were determined and were found to be just as great following exercise after sodium bicarbonate as they were following exercise alone.

Ammonium Chloride.—Acidosis was produced in three experiments upon two subjects by the ingestion of single large doses of ammonium chloride (15, 20, and 25 gm.). Table III and Figs. 10 and 11 show the results. The acidosis was quite mild. In one experiment (Exp. 17) the T-waves became taller in all three leads. In the other two experiments control electrocardiograms were not obtained, but the height of the T-waves was considerably greater than their average height in a large number of control curves taken at different times for other experiments. Indeed, in one experiment the T-waves became taller than the tallest T-deflections of a large number of control curves on this subject. In the other experiment the height of T, while greater than the average, did not exceed the tallest T-waves of the various control curves on this subject. There were no significant changes in the R-waves.

Rebreathing.—In one experiment the subject rebreathed into the common type of vital capacity spirometer for five and one-half minutes. At this point the shortness of breath was unbearable. No specimens of blood were taken, but there is no doubt that a moderate acidosis was produced. The T-waves became slightly taller in all leads. The R-waves became slightly smaller in Lead I and taller in Leads II and III (Table III). The electrocardiographic changes were probably too slight to be of significance, except that the T-waves did not become smaller during excessive breathing comparable to that which produced alkalosis in the experiments upon voluntary overventilation.

The effects of atropine sulfate (1.3 mg. intravenously) and of epinephrin (0.6 mg. subcutaneously) were observed in each of two subjects. In none of these experiments did the T-waves undergo significant changes. This is of interest in that the T-waves did not become taller, as they did when the heart rate and blood pressure were increased after exercise.

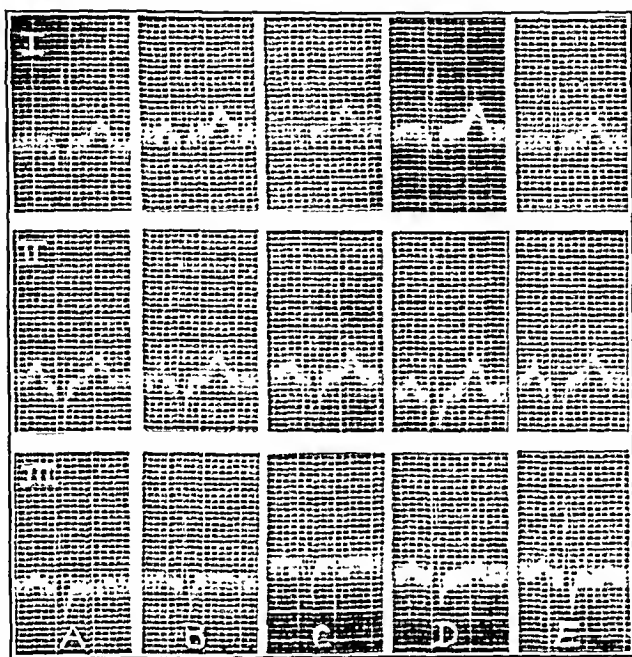


Fig. 10.—Experiment 18, subject B. A, control. B, C, and D, at intervals of approximately two hours following the ingestion of 15 gm. of ammonium chloride. E, twenty-four hours later. Slight acidosis was produced (see Fig. 11).

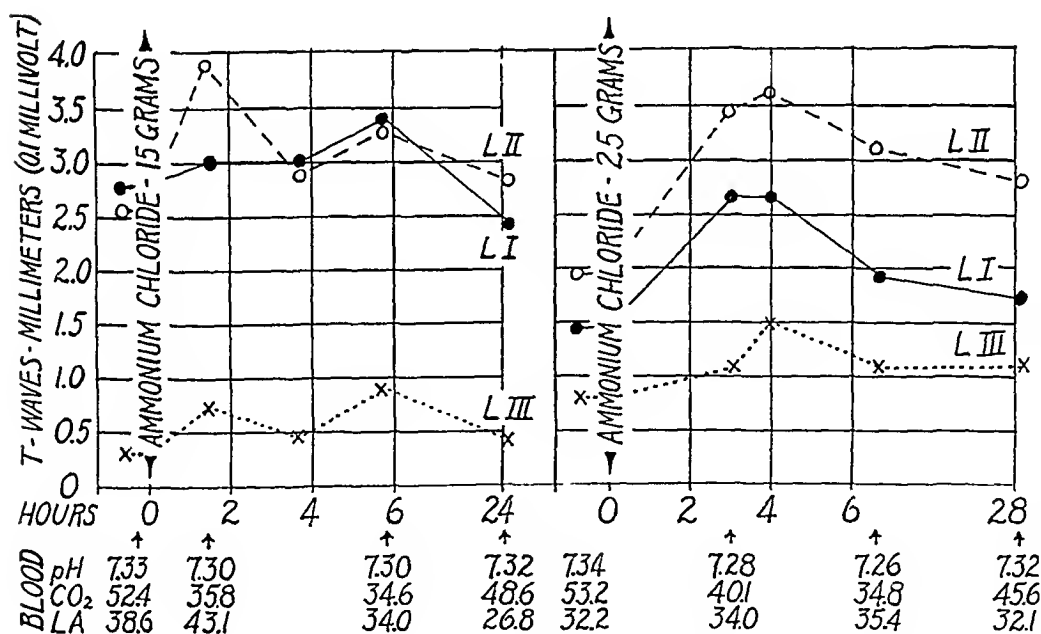


Fig. 11.—Experiment 18, subject B. Ingestion of 15 gm. of ammonium chloride. Experiment 31, subject A. Ingestion of 25 gm. of ammonium chloride. In this experiment no control observations were made. The values represented are the averages of many control observations on this subject.

Spontaneous Changes.—Two subjects served for five experiments in which they rested quietly while curves were taken at five-minute intervals. These showed slight spontaneous variations in the amplitudes of the T-waves, which, however, were not uniform in direction, and were smaller in magnitude than the changes accompanying the various experimental procedures previously described. Similarly, each subject who served for more than one experiment showed in his control curves slight variations in the amplitude of T. These, likewise, were not so pronounced as the changes induced experimentally, nor did they seem related to the slight variations in the pH or in the CO₂ combining power of the control specimens of blood.

COMMENT

While there was no direct quantitative relationship between the amplitudes of the T-waves and the degree of alkalosis or acidosis, the observations indicate that alkalosis is accompanied by a decrease and acidosis by an increase in the amplitudes of the T-waves. The results were consistent throughout the series of experiments, with only one exception. The changes in height of T were usually, but not always, more pronounced than the variations occurring spontaneously. The T-waves, however, were consistently smaller with alkalosis and taller with acidosis, and this is considered significant.

The clinical application of these observations is probably quite limited. Pronounced degrees of acidosis and alkalosis are relatively uncommon, and it is decidedly unusual to obtain electrocardiograms in such conditions. By chance, however, a curve was taken on a young woman with a normal heart who complained of palpitation shortly after the intravenous administration of sodium bicarbonate for the treatment of migraine. The curve showed strikingly inverted T-waves. On the following day the curve was normal. We have not chanced upon or recognized electrocardiographic changes which could be attributed to alkalosis or acidosis in other patients. It is not unlikely, however, that such changes may occasionally pass unrecognized.

It is not apparent why or how alkalosis and acidosis modify the electrocardiogram. The duration of systole must be altered locally, possibly to different degrees in different parts of the heart. This might be revealed by changes in the Q-T interval.

The total duration of electrical systole was determined by measuring from the beginning of the Q-R-S deflections to the end of the T-waves, and then employing the formula of Bazett,¹⁰ which takes into account the influence of the cardiac rate: $\text{systole} = K \sqrt{\text{cycle}}$ (Table IV). During the tetany of experimental overventilation the records were too distorted by tremor to permit accurate measurements, but K was slightly increased in the patient with hysterical overbreathing, and after the ingestion of sodium bicarbonate, after exercise, after the ingestion of

ammonium chloride, and after atropine. Overbreathing into a large dead space caused no significant change in K.

In some of the experiments serum calcium determinations were made. The changes in the duration of systole were usually, but not always, inversely related to the changes in serum calcium.¹¹⁻¹⁵ When the values for K and for the serum calcium were both increased, it would seem likely that the changes in the total serum calcium value did not truly represent changes in the ionized or physiologically active calcium.¹⁶

TABLE IV

THE EFFECTS OF VARIOUS PROCEDURES UPON THE Q-T INTERVAL

Expressed as K of Bazett's Formula: systole = $K \sqrt{\text{cycle}}$

EXP.	SUBJECT	PROCEDURE	BEFORE	DURING*	AFTER
12	Patient	Overventilation	0.343	0.384	0.370
13	B	Overventilation with dead space	0.415	0.406	0.377
26	B	Overventilation with dead space	0.389	0.400	0.402
35	A	Overventilation with dead space	0.412	0.413	0.397
27	A	Rebreathing	0.400	0.400	0.412
28	A	Sodium bicarbonate	0.428	0.437	0.411
14	A	Sodium bicarbonate	0.397	0.432	0.425
3	B	Sodium bicarbonate	0.429	0.425	----
4	E	Sodium bicarbonate	0.388	0.398	----
30	F	Sodium bicarbonate	0.394	0.436	0.382
16	A	Exercise	0.401	0.430	0.407
5	B	Exercise	0.407	0.432	0.414
6	F	Exercise	0.387	0.392	0.380
31	G	Exercise	0.394	0.404	0.401
18	A	Ammonium chloride	----	0.425	0.413
	B	Ammonium chloride	0.380	0.388	0.400

*Curves were taken immediately after exercise.

The changes in the duration of electrical systole which we have observed were of small magnitude and of doubtful significance (Table IV). If they have any significance, they suggest that the changes in the duration of electrical systole, which must have occurred locally in the ventricles, consisted in a prolongation rather than a reduction.

SUMMARY AND CONCLUSIONS

Pronounced flattening of the T-waves was observed in a patient with hysterical overventilation and tetany. This prompted an experimental investigation of the effects of alkalosis and acidosis upon the human electrocardiogram.

Alkalosis, produced by voluntary overventilation or by the ingestion of sodium bicarbonate, is accompanied by a reduction in the amplitude of T.

Acidosis, produced by exercise or by the ingestion of ammonium chloride, is accompanied by an increase in the amplitude of T.

While the clinical application of these observations is probably quite limited, they may offer an explanation for occasional electrocardiographic changes not otherwise understood.

REFERENCES

1. Einthoven, W., Fahr, G., and de Waart, A.: Über die Richtung und die manifeste Grösse der Potentialschwankungen im menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, *Pflüger's Arch. f. d. ges. Physiol.* 150: 275, 1913.
2. Wilson, Frank N., and Finch, Russell: The Effect of Drinking Iced-Water Upon the Form of the T Deflection of the Electrocardiogram, *Heart* 10: 275, 1923.
3. Samojloff, A.: Weitere Beiträge zur Elektrophysiologie des Herzens, *Pflüger's Arch. f. d. ges. Physiol.* 135: 417, 1910.
4. Rothberger, J., and Winterberg, H.: Über die Beziehungen der Herznerven zur Form des Elektrokardiogramms, *Pflüger's Arch. f. d. ges. Physiol.* 135: 506, 1910.
5. Cohn, Alfred E., and Raisbeck, Milton J.: An Investigation of the Relation of the Position of the Heart to the Electrocardiogram, *Heart* 9: 311, 1922.
6. Schott, E.: Die Veränderung der Form des Elektrokardiogramms unter der Wirkung von Säure, Alkali, und Methylenblau, *Deutsches Arch. f. klin. Med.* 152: 287, 1926.
7. Kronenberger, F., and Ruffin, H.: Herzstromkurve und vegetatives Nervensystem mit besonderer Berücksichtigung der Hyperventilationstetanie. *Deutsches Arch. f. klin. Med.* 165: 257, 1929.
8. McCance, R. A.: Spontaneous Overbreathing Tetany, *Quart. J. Med.* 25: 247, 1932.
9. Simpson, Walter M.: Studies on the Physiology of Fever, *J. A. M. A.* 106: 246, 1936.
10. Bazett, H. C.: An Analysis of the Time-Relations of Electrocardiograms, *Heart* 7: 353, 1920.
11. Carter, E. P., and Andrus, E. C.: Q-T Interval in the Human Electrocardiogram in the Absence of Cardiac Disease, *J. A. M. A.* 78: 1922, 1922.
12. White, Paul D., and Mudd, Seeley G.: Observations on the Effect of Various Factors on the Duration of the Electrical Systole of the Heart as Indicated by the Length of the Q-T Interval of the Electrocardiogram, *J. Clin. Investigation* 7: 387, 1929.
13. Hecht, H., and Korth, C.: Über Wesen und Bedeutung des Q-T Intervalles im Elektrokardiogramm, *Ztschr. f. Kreislaufforsch.* 29: 577, 1937.
14. Barker, Paul S., Johnston, Franklin D., and Wilson, Frank N.: The Duration of Systole in Hypocalcemia, *AM. HEART J.* 14: 82, 1937.
15. Kellog, F., and Kerr, Wm. J.: Electrocardiographic Changes in Hyperparathyroidism, *AM. HEART J.* 12: 346, 1936.
16. Grant, S. B., and Goldman, A.: A Study of Forced Respiration: Experimental Production of Tetany, *Am. J. Physiol.* 52: 209, 1920.
17. Barr, D. P., Himwich, H. E., and Green, R. P.: Studies in the Physiology of Muscular Exercise. I. Changes in Acid-Base Equilibrium Following Short Periods of Vigorous Muscular Exercise, *J. Biol. Chem.* 55: 495, 1923.
18. Barr, D. P., and Himwich, H. E.: Studies in the Physiology of Muscular Exercise. III. Development and Duration of Changes in Acid-Base Equilibrium, *J. Biol. Chem.* 55: 539, 1932.

STUDIES ON MERCURIAL DIURESIS

II. THE IMMEDIATE EFFECT ON THE VENOUS BLOOD PRESSURE

ITALO F. VOLINI, M.D., AND ROBERT O. LEVITT, M.D.

CHICAGO, ILL.

CONSIDERABLE improvement is noted by patients with heart failure following diuresis induced by the organic mercurial diuretics. Dyspnea is often noticeably ameliorated. Reduction of edema and weight loss are the most important objective evidences, although an increase in the vital capacity may also occur. We wish to point out that a reduction of the high venous blood pressure is another objective sign of betterment.

The clinical significance of the venous blood pressure has probably not obtained the attention it deserves. Lewis stresses its importance but, like Wiggers, indicates that simple inspection of the veins yields just as accurate information as direct measurement. Great discrepancies, however, are frequently found between the results obtained by inspection, and by indirect and direct methods of measurement. We believe, as does Fishberg, that the latter method has the least potentialities for inaccuracy; the principal objection to it is the necessity for venepuncture. Variations induced by changes in the degree of heart failure can be readily followed by direct measurement.

Readings of the venous pressure above the upper limit of normal indicate cardiac insufficiency in cases in which the presence of mediastinal masses and mechanical obstruction are ruled out. The high readings are pathognomonic of right-sided heart failure. As left ventricular failure is the most frequent cause of right-sided heart failure, high venous pressure then indicates left-sided insufficiency also.

Fishberg describes the systemic veins as a reservoir filled from the periphery by blood from the capillaries and emptied by the cardiac pump; normally, the intake and emptying mechanisms are in dynamic equilibrium. The venous pressure affords a measure of the filling of the reservoir. If the right side of the heart is insufficient, the reservoir fills and the venous pressure rises. If the peripheral vessels allow little blood to pass into the larger veins the level of the reservoir, and, with it, the venous pressure, falls. Many factors, cardiac and extracardiac, tend to regulate the venous pressure in the normal individual. The investigation reported in this paper was undertaken to obtain measurements, by the direct method, of the changes in venous pressure produced by mercurial diuresis in patients suffering from marked circulatory failure with pronounced edema.

From the Cook County Hospital, Chicago, and The Department of Medicine, Loyola University School of Medicine.

This investigation was aided by a grant from Ciba Pharmaceutical Products, Inc.
Received for publication Aug. 1, 1938.

TABLE I

NO.	PATIENT	DATE	ARTERIAL BLOOD PRESSURE	VENOUS BLOOD PRESSURE	DROP IN VENOUS BLOOD PRESSURE	URINARY OUTPUT	DIURETIC
1.	T. R.	3/22 3/23	130/100 138/88	220 mm. 156 mm.	64 mm.	1400 c.c. 2500 c.c.	Esidrone 1 c.c.
2.	T. R.	3/26 3/27	130/86 136/94	242 mm. 136 mm.	106 mm.	1000 c.c. 2900 c.c.	Esidrone 1 c.c.
3.	J. S.	3/15 3/16	122/84 122/84	156 mm. 72 mm.	84 mm.	2000 c.c. 4000 c.c.	Esidrone 2 c.c.
4.	J. S.	3/18 3/19	118/74 112/74	125 mm. 77 mm.	48 mm.	500 c.c. 5000 c.c.	Esidrone 2 c.c.
5.	J. S.	3/26 3/27	132/104 110/86	228 mm. 176 mm.	48 mm.	500 c.c. 3200 c.c.	Esidrone 2 c.c.
6.	J. S.	3/29 3/30	118/84 106/74	142 mm. 102 mm.	40 mm.	750 c.c. 2500 c.c.	Esidrone 2 c.c.
7.	J. M.	3/10 3/11		162 mm. 112 mm.	50 mm.	400 c.c. 2200 c.c.	Esidrone 1 c.c.
8.	J. M.	3/14 3/15	212/140 146/90	80 mm. 70 mm.	10 mm.	1000 c.c. 1800 c.c.	Esidrone 1 c.c.
9.	J. M.	3/21 3/22	132/78 135/70	170 mm. 100 mm.	70 mm.	1300 c.c. 2000 c.c.	Esidrone 1 c.c.
10.	J. M.	3/26 3/27	124/78 138/78	172 mm. 160 mm.	12 mm.	500 c.c. 3500 c.c.	Esidrone 1 c.c.
11.	J. M.	3/29 3/30	122/70 112/68	52 mm. 30 mm.	22 mm.	2900 c.c. 2900 c.c.	Esidrone 1 c.c.
12.	W. S.	3/9 3/10	128/88 126/86	358 mm. 288 mm.	70 mm.	1900 c.c. 3000 c.c.	Esidrone 2 c.c.
13.	W. S.	3/14 3/15	125/85 125/90	410 mm. 236 mm.	174 mm.	700 c.c. 5000 c.c.	Esidrone 2 c.c.
14.	W. S.	3/18 3/19	110/84 102/66	315 mm. 192 mm.	123 mm.	600 c.c. 4400 c.c.	Esidrone 2 c.c.
15.	W. S.	3/22 3/23	128/88 128/88	154 mm. 80 mm.	74 mm.	1300 c.c. 3500 c.c.	Esidrone 2 c.c.
16.	W. S.	4/14 4/15		358 mm. 300 mm.	58 mm.	300 c.c. 2400 c.c.	Esidrone 1 c.c.
17.	W. S.	4/17 4/18		286 mm. 274 mm.	12 mm.	700 c.c. 2200 c.c.	Esidrone 1 c.c.
18.	W. S.	4/20 4/21		224 mm. 166 mm.	58 mm.	800 c.c. 2400 c.c.	Esidrone 2 c.c.
19.	W. S.	5/16 5/17		340 mm. 212 mm.	128 mm.	800 c.c. 5300 c.c.	Esidrone 1 c.c.
20.	W. S.	5/20 5/21		270 mm. 246 mm.	24 mm.	1100 c.c. 3800 c.c.	Esidrone 1 c.c.
21.	W. S.	5/25 5/26		274 mm. 216 mm.	58 mm.	1000 c.c. 3300 c.c.	Esidrone 1 c.c.
22.	W. S.	5/31 6/1		384 mm. 340 mm.	44 mm.	900 c.c. 4500 c.c.	Esidrone 2 c.c.
23.	W. S.	6/4 6/5		390 mm. 264 mm.	126 mm.	500 c.c. 4300 c.c.	Esidrone 2 c.c.
24.	H. D.	5/3 5/4		200 mm. 180 mm.	20 mm.	900 c.c. 4500 c.c.	Esidrone 1 c.c.
25.	H. D.	5/7 5/8		198 mm. 200 mm.	+2 mm.	1000 c.c. 3600 c.c.	Esidrone 1 c.c.
26.	H. D.	5/10 5/11		250 mm. 176 mm.	74 mm.	700 c.c. 2600 c.c.	Esidrone 1 c.c.

TABLE I—CONT'D

NO.	PATIENT	DATE	ARTERIAL BLOOD PRESSURE	VENOUS BLOOD PRESSURE	DROP IN VENOUS BLOOD PRESSURE	URINARY OUTPUT	DIURETIC
27.	H. D.	5/14 5/15		216 mm. 152 mm.	64 mm.	800 c.c. 3000 c.c.	Esidrone 1 c.c.
28.	H. D.	5/19 5/20		170 mm. 86 mm.	84 mm.	500 c.c. 3800 c.c.	Esidrone 1 c.c.
29.	H. D.	5/22 5/23		200 mm. 77 mm.	123 mm.	1000 c.c. 2000 c.c.	Esidrone 2 c.c.
30.	J. E.	4/14 4/15		160 mm. 140 mm.	20 mm.	1250 c.c. 2600 c.c.	Esidrone 1 c.c.
31.	J. E.	4/18 4/19		188 mm. 128 mm.	60 mm.	700 c.c. 1650 c.c.	Esidrone 1 c.c.
32.	B. C.	4/15 4/16		274 mm. 204 mm.	70 mm.	1000 c.c. 2000 c.c.	Esidrone 1 c.c.
33.	B. C.	4/18 4/19		208 mm. 164 mm.	44 mm.	700 c.c. 3200 c.c.	Esidrone 1 c.c.
34.	B. C.	4/21 4/22		200 mm. 170 mm.	30 mm.	500 c.c. 2200 c.c.	Esidrone 1 c.c.
35.	B. C.	4/28 4/29		186 mm. 166 mm.	20 mm.	600 c.c. 2600 c.c.	Esidrone 2 c.c.
36.	B. C.	5/3 5/4		200 mm. 106 mm.	94 mm.	400 c.c. 3400 c.c.	Esidrone 2 c.c.
37.	B. C.	6/24 6/25		272 mm. 198 mm.	74 mm.	500 c.c. 2500 c.c.	Esidrone 1 c.c.
38.	B. C.	7/11 7/12		210 mm. 130 mm.	80 mm.	800 c.c. 7000 c.c.	Esidrone 2 c.c.
39.	C. A.	4/26 4/27		352 mm. 330 mm.	22 mm.	100 c.c. 1800 c.c.	Esidrone 1 c.c.
40.	C. A.	5/2 5/3		332 mm. 240 mm.	90 mm.	1000 c.c. 4000 c.c.	Esidrone 1 c.c.
41.	C. A.	5/6 5/7		350 mm. 182 mm.	168 mm.	1000 c.c. 4000 c.c.	Esidrone 1 c.c.
42.	C. A.	5/10 5/11		172 mm. 116 mm.	56 mm.	800 c.c. 4000 c.c.	Esidrone 1 c.c.
43.	C. A.	6/5 6/6		248 mm. 164 mm.	84 mm.	800 c.c. 4000 c.c.	Esidrone 1 c.c.
44.	T. P.	4/24 4/25		315 mm. 176 mm.	139 mm.	600 c.c. 5800 c.c.	Esidrone 1 c.c.
45.	T. P.	4/30 5/1		254 mm. 120 mm.	134 mm.	1000 c.c. 3000 c.c.	Esidrone 1 c.c.
46.	F. M.	4/21 4/22		266 mm. 226 mm.	40 mm.	200 c.c. 4000 c.c.	Esidrone 1 c.c.
47.	F. M.	7/5 7/6		330 mm. 240 mm.	90 mm.	700 c.c. 4900 c.c.	Esidrone 1 c.c.
48.	A. F.	4/19 4/20		320 mm. 276 mm.	44 mm.	500 c.c. 5300 c.c.	Esidrone 2 c.c.
49.	A. F.	4/21 4/22		310 mm. 296 mm.	14 mm.	800 c.c. 4000 c.c.	Esidrone 2 c.c.
50.	A. F.	4/25 4/26		364 mm. 306 mm.	58 mm.	1800 c.c. 4000 c.c.	Esidrone 2 c.c.
51.	A. F.	4/29 4/30		330 mm. 248 mm.	82 mm.	1100 c.c. 5300 c.c.	Esidrone 2 c.c.
52.	A. F.	5/7 5/6		300 mm. 176 mm.	124 mm.	1200 c.c. 8300 c.c.	Esidrone 2 c.c.

TABLE I—CONT'D

NO.	PATIENT	DATE	ARTERIAL BLOOD PRESSURE	VENOUS BLOOD PRESSURE	DROP IN VENOUS BLOOD PRESSURE	URINARY OUTPUT	DIURETIC
53.	A. F.	5/16 5/17		270 mm. 226 mm.	44 mm.	1000 c.c. 1800 c.c.	Esidrone 1 c.c.
54.	A. F.	5/20 5/21		274 mm. 220 mm.	54 mm.	700 c.c. 1900 c.c.	Esidrone 2 c.c.
55.	A. F.	5/27 5/28		278 mm. 216 mm.	62 mm.	300 c.c. 3500 c.c.	Esidrone 1 c.c.
56.	A. F.	5/31 6/1		274 mm. 250 mm.	24 mm.	300 c.c. 3000 c.c.	Esidrone 2 c.c.
57.	A. F.	6/15 6/16		286 mm. 194 mm.	92 mm.	1500 c.c. 5700 c.c.	Esidrone 2 c.c.
58.	A. F.	6/20 6/21		208 mm. 160 mm.	48 mm.	1300 c.c. 6000 c.c.	Esidrone 2 c.c.
59.	A. F.	6/27 6/28		156 mm. 92 mm.	64 mm.	1200 c.c. 4600 c.c.	Esidrone 2 c.c.
60.	A. F.	7/1 7/2		128 mm. 98 mm.	30 mm.	1200 c.c. 4600 c.c.	Esidrone 2 c.c.
61.	A. S.	6/22 6/23		274 mm. 272 mm.	32 mm.	400 c.c. 2200 c.c.	Esidrone 1 c.c.
62.	A. S.	6/27 6/28		330 mm. 250 mm.	80 mm.	200 c.c. 2600 c.c.	Esidrone 1 c.c.
63.	A. S.	7/5 7/6		288 mm. 204 mm.	84 mm.	700 c.c. 2000 c.c.	Esidrone 1 c.c.
64.	J. T.	5/5 5/6		170 mm. 88 mm.	82 mm.	650 c.c. 3200 c.c.	Esidrone 1 c.c.
65.	J. T.	6/5 6/6		232 mm. 170 mm.	62 mm.	400 c.c. 1000 c.c.	Esidrone 1 c.c.
66.	J. T.	6/15 6/16		140 mm. 118 mm.	22 mm.	50 c.c. 1400 c.c.	Esidrone 1 c.c.
67.	F. B.	4/22 4/23		266 mm. 76 mm.	190 mm.	200 c.c. 3300 c.c.	Esidrone 1 c.c.
68.	W. L.	4/17 4/18		256 mm. 126 mm.	130 mm.	600 c.c. 4000 c.c.	Esidrone 1 c.c.
69.	F. L.	4/15 4/16		220 mm. 74 mm.	146 mm.	1600 c.c. 3500 c.c.	Esidrone 1 c.c.
70.	C. S.	4/26 4/27		302 mm. 148 mm.	154 mm.	800 c.c. 4000 c.c.	Esidrone 1 c.c.
71.	J. S.	4/15 4/16		220 mm. 104 mm.	116 mm.	1900 c.c. 2800 c.c.	Esidrone 2 c.c.
72.	J. H.	5/16 5/17		74 mm. 40 mm.	34 mm.	900 c.c. 1900 c.c.	Esidrone 1 c.c.
73.	J. S.	5/16 5/17		244 mm. 150 mm.	94 mm.	1300 c.c. 4500 c.c.	Esidrone 1 c.c.
74.	J. C.	5/27 5/28		112 mm. 76 mm.	36 mm.	2000 c.c. 3500 c.c.	Esidrone 1 c.c.
75.	N. H.	5/16 5/17		94 mm. 72 mm.	22 mm.	900 c.c. 1900 c.c.	Esidrone 1 c.c.
76.	W. H.	5/16 5/17		90 mm. 70 mm.	20 mm.	400 c.c. 1900 c.c.	Esidrone 1 c.c.
77.	F. C.	6/11 6/12		84 mm. 64 mm.	20 mm.	500 c.c. 2000 c.c.	Esidrone 1 c.c.
78.	C. F.	6/22 6/23		130 mm. 90 mm.	40 mm.	400 c.c. 1500 c.c.	Esidrone 1 c.c.
79.	W. L.	7/6 7/7		254 mm. 100 mm.	154 mm.	1700 c.c. 5000 c.c.	Esidrone 1 c.c.

METHOD OF STUDY

The direct manometric method, using an 18-gauge needle in the antecubital vein, was employed, with 3 per cent sodium citrate solution as the anticoagulant. The arm position recommended by Griffith, Chamberlin and Kitchell in their modification of the Moritz and Tabora technique was selected. The normal variations of venous pressure by this method range between 60 and 120 mm. of water. We recognize the difficulty in making precise correction for the zero reference point, but believe that the level of the auricle can be readily estimated for the hydrostatic pressure equilibration. However, adduction of the arm was not complete, and slight flexion, in supination, at the elbow was permitted, thus obviating the objections raised by Brandt and Katz.

All patients studied were placed on our cardiac regime, consisting of rest in bed and a diet of 1683 calories (carbohydrate 215 gm., protein 55 gm., fat 67 gm., sodium chloride 0.985 gm.) with a total twenty-four-hour fluid intake of 1600 c.c., including the calculated water content of foods. Potassium chloride was given at meals. Digitalis and ammonium chloride were used in most of the cases, with morphine and phenobarbital when necessary. A control period of three days generally preceded the initiation of mercurial diuresis. The weight and twenty-four-hour urinary output were recorded daily. The venous blood pressure was measured by the direct method on admission, three days later, before the injection of the mercurial diuretic, and again twenty-four hours later. All readings were made at the same hour in the morning. Subsequent determinations were made before, and twenty-four hours following, the administration of the diuretic. The diuretic employed was esidrone (Ciba), the sodium salt of pyridinedicarboxy- β -mercuri- ω hydroxypropylamide-theophylline, which contains 31.2 per cent of mercury in nonionizable form and 28 per cent of theophylline which is bound chemically to the mercury molecule. It is a stable, neutral, crystalline substance which is readily soluble in water. We have reported the remarkable effectiveness of esidrone in a previous communication. In this study esidrone was administered intravenously in doses of 1 or 2 c.c.; each cubic centimeter contains 0.14 gm. of the drug, which equals 0.043 gm. of mercury.

Table I summarizes the venous blood pressure readings in seventy-nine patients before, and twenty-four hours after, the intravenous injection of esidrone. The highest pressure in the series was 410 mm. The maximum drop in twenty-four hours following administration of the diuretic was 174 mm. (from 410 mm. to 236 mm.). The average drop was 70 mm. One patient showed a rise of 2 mm. despite an output of 3600 c.c. In all of the others there was a decrease, as Table I demonstrates. It is to be remarked that all of the patients had pronounced edema, which accounts for the large outputs. Included in the group were cases of hypertensive and arteriosclerotic, rheumatic, syphilitic, and thyrotoxic, heart disease, and chronic cor pulmonale.

DISCUSSION

We have found very little variation in the abnormal venous blood pressure readings in edematous patients unless pronounced diuresis occurs. The following examples (Table II) illustrate this point.

TABLE II

	URINARY OUTPUT	VENOUS BLOOD PRESSURE	COMMENT
<i>F. M.</i>			
7/ 3/38	300 c.c.	296 mm.	
7/ 4/38	200 c.c.	346 mm.	
7/ 5/38	300 c.c.	330 mm.	
7/ 6/38	4900 c.c.	240 mm.	Esidrone 1 c.c.
<i>W. M.</i>			
7/ 2/38	700 c.c.	366 mm.	
7/ 3/38	860 c.c.	336 mm.	
7/ 4/38	580 c.c.	330 mm.	
7/ 5/38	1800 c.c.	260 mm.	Spontaneous diuresis
7/ 6/38	1700 c.c.	254 mm.	Spontaneous diuresis
7/ 7/38	5000 c.c.	100 mm.	Esidrone 1 c.c.
<i>E. A.</i>			
7/22/38	600 c.c.	330 mm.	
7/23/38	1000 c.c.	320 mm.	
7/24/38	700 c.c.	340 mm.	

It will be observed that diuresis is associated with the drop in venous blood pressure, and that the fall is directly proportional to the degree of diuresis. When relatively slight spontaneous diuresis occurs the drop in the venous pressure is relatively small, whereas with the pronounced diuresis produced by esidrone the drop in the venous blood pressure is much more pronounced. A large spontaneous diuresis naturally produces the same result. These statements apply to the immediate effects at the end of twenty-four hours. In cases in which improvement continued as a result of general cardiac management and repeated injections of the diuretic, the venous blood pressure continued to descend until it reached normal values. However, a rise generally occurred after the diuresis subsided, although the previous high levels were not attained unless the edema became more pronounced or the heart failure more severe.

These observations indicate that the venous blood pressure falls as diuresis occurs. The cause of the decrease may be ascribed to one or several factors. The pressure of edema fluid surrounding the peripheral veins decreases with diuresis, thus increasing the capacity of the veins. This lowers the venous blood pressure by permitting relaxation. Second, it may be that the heart muscle itself is edematous; if so, a reduction of this edema should increase its efficiency. Third, the increase in vital capacity which follows the diuresis means that intrathoracic pressure is more negative, with the result that blood flow into the thorax is facilitated. Again, the reduction of edema in and about the peripheral muscles improves the efficiency of muscle contraction, which is an important factor in venous flow. In another communication we shall present evidence to indicate that diuresis influences the central nervous system, and therefore the central venopressor regulating mechanism.

SUMMARY AND CONCLUSIONS

The immediate effect of mercurial diuresis (and also of copious spontaneous diuresis) on the venous blood pressure is to produce a decrease. The drop in venous pressure is apparently directly proportional to the degree of diuresis. This fall in venous pressure is an objective measure of clinical improvement in the treatment by mercurial diuretics of patients with heart failure and edema.

REFERENCES

1. Lewis, Thomas: *Diseases of the Heart*, New York, 1933, The Macmillan Company.
2. Wiggers, C. J.: *Physiology in Health and Disease*, Ed. 2, Philadelphia, 1937, Lea and Febiger.
3. Fishberg, A.: *Heart Failure*, Philadelphia, 1937, Lea and Febiger.
4. Moritz, F., and von Tabora, D.: Über eine Methode, beim menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsch. Arch. f. klin. Med.* 98: 475, 1910.
5. Griffith, G. C., Chamberlin, C. T., and Kitchell, Jr.: A Simplified Apparatus for Direct Venous Pressure Determination, Modified From Moritz and von Tabora, *Am. J. M. Sc.* 187: 371, 1934.
6. Griffith, G. C., Chamberlin, C. T., and Kitchell, Jr.: Observations on the Practical Significance of Venous Pressure in Health and Disease, With a Review of the Literature, *Am. J. M. Sc.* 187: 643, 1934.
7. Brandt, F., and Katz, G.: Über die paradoxen Atemschwankungen des Venendruckes beim Menschen, *Ztschr. f. d. ges. Exper. Med.* 76: 158, 1931.
8. Eyster, J. A. E.: Venous Pressure in Cardiac Decompensation, *J. A. M. A.* 89: 428, 1927.
9. Eyster, J. A. E.: Venous Pressure, *J. A. M. A.* 97: 1269, 1931.
10. Henderson, Y.: The Volume of the Circulation and Its Regulation by the Venopressor Mechanism, *J. A. M. A.* 97: 1265, 1931.
11. Halbrook, A. A.: Normal Venous Pressure, *Am. J. M. Sc.* 195: 751, 1938.
12. Brams, W. A.: Venous Pressure, *M. Clin. North America* 19: 1273, 1936.
13. Greene, J. A., Paul, W. D., and Feller, A. E.: Action of Theophylline and Ethylenediamine on Intrathecal and Venous Pressure in Cardiac Failure and on Bronchial Obstruction in Cardiac Failure and in Bronchial Asthma, *J. A. M. A.* 109: 1712, 1937.
14. Volini, I. F., and Levitt, R. O.: Studies on Mercurial Diuresis. I. Esidrone, a New Mercurial Diuretic, *Illinois M. J.* 74: 355, 1938.

PLETHYSMOGRAPHIC STUDIES OF PERIPHERAL BLOOD FLOW IN MAN

I. CRITERIA FOR OBTAINING ACCURATE PLETHYSMOGRAPHIC DATA*

DAVID I. ABRAMSON, M.D.,† HERMAN ZAZEELA, M.D., AND
JOSEPH MARRUS, B.S.
CINCINNATI, OHIO

THE problem of blood flow in the extremities under various physiologic and pathologic states has recently been subjected to further investigation. The studies generally have employed the plethysmograph, although occasionally the indirect calorimetric method^{1, 2} has been substituted. With the latter, the extremity is immersed in a known volume of water and the amount of heat given off in a definite period of time is measured by noting the increase in the temperature of the water. With the former method, the extremity is inserted into a plethysmograph and the initial rate of swelling of the limb recorded when a collecting pressure is applied, i.e., one sufficient to occlude venous outflow without interfering with arterial inflow. The principle underlying this procedure was utilized by Brodie³ for determining blood flow through an organ, and was then modified by Hewlett and van Zwaluwenburg⁴ for similar measurements in an extremity. The method was not widely employed until recently, when Freeman⁵ modified it somewhat to measure blood flow in the hand. Numerous investigators have made use of the hand plethysmograph in various physiologic experiments,⁶⁻⁹ while others have worked with a similar type of apparatus for measuring blood flow through the forearm¹⁰⁻¹² and the foot.^{6, 12}

Critical perusal of the pertinent literature reveals a marked variation in the absolute blood flow figures for apparently normal subjects. In fact, great differences have been observed in the same individual on different days, a finding which is probably due in part to normal variations in cardiac output. Most investigators either state or imply that conditions must be controlled rigidly if any significance is to be attached to such results. However, these conditions and the manner of controlling them are generally only casually mentioned, or not in sufficient detail to be of help in guiding a beginner in the field.

Since interest in peripheral vascular disease continues to increase, and since the method of choice in the study of this subject will most likely

*From the Medical Service of B. S. Oppenheimer, Mt. Sinai Hospital, New York, and the Institute for Medical Research, The Jewish Hospital, Cincinnati, Ohio.

Aided in part by the Samuel and Regina Kuhn Fund.

†Work done in part during tenure of the Richard and Ella Hunt Sutro Fellowship. Received for publication August 8, 1938.

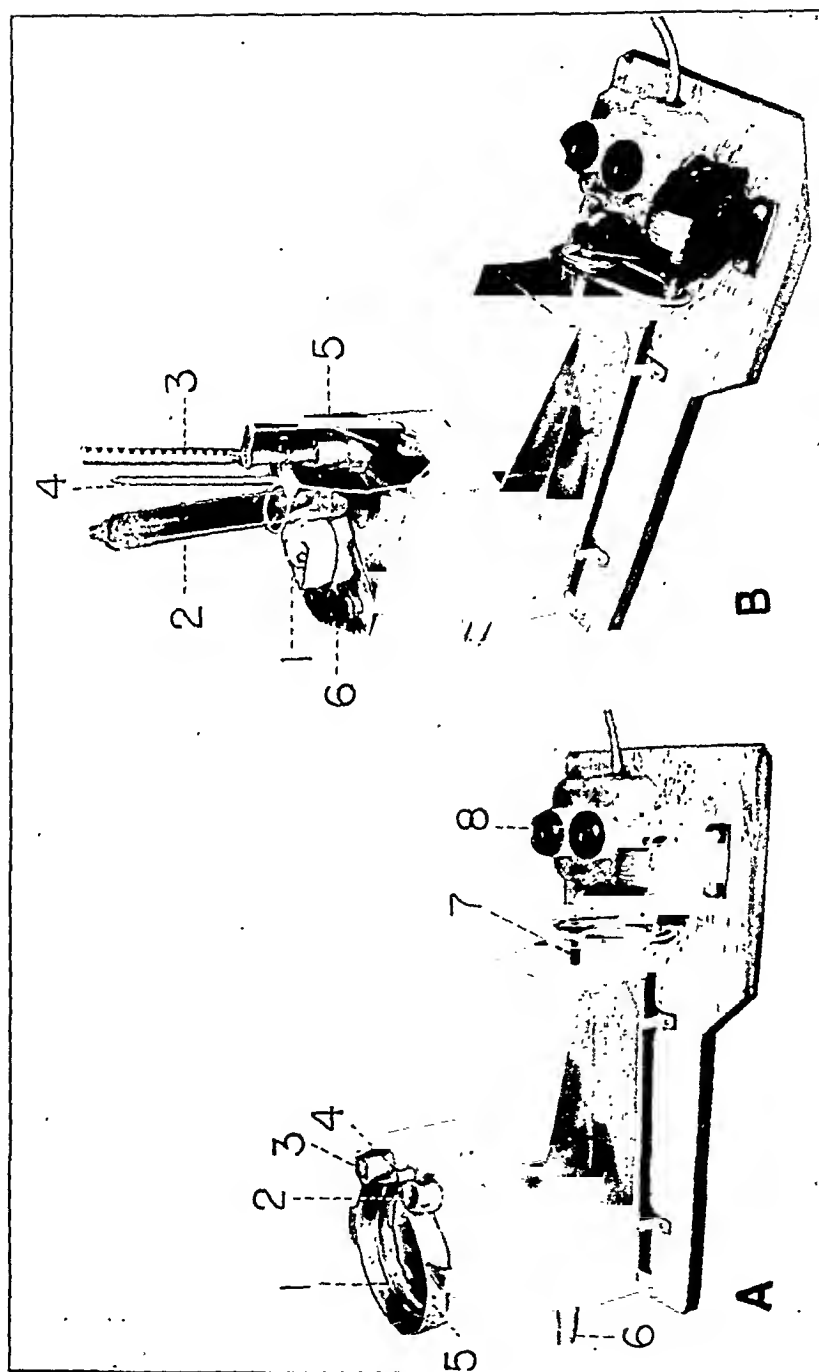


Fig. 1.—Photographs of foot plethysmograph. *A*, 1, thermometer; 2, support for glass tube; 3, outlet tube; 4, opening for water removal; 5, rubber euff; 6, wide glass tube; 7, propeller; 8, switches for propeller and electric heater. *B*, 1, thermometer; 2, support for glass tube and burette; 3, outlet tube; 4, opening for water removal; 5, rubber euff; 6, wide glass tube; 7, propeller; 8, switches for propeller and electric heater.

involve the further use of the plethysmograph, it was considered advisable to investigate in detail the various mechanical and physical difficulties which must be overcome before constant and reliable blood flow data can be obtained. The purpose of the present report is to describe those conditions which may lead to the production of artifacts, and the means utilized to correct or eliminate them. In all instances, blood flow figures for the foot were obtained simultaneously with those for either the hand or forearm.

DESCRIPTION OF PLETHYSMOGRAPHS AND OF PRELIMINARY PREPARATION FOR BLOOD FLOW DETERMINATIONS

Foot Plethysmograph.—The foot plethysmograph (Fig. 1) consists of two containers of brass or monel metal (one fitted into the other so as to form an insulated space) which are made grossly in the shape of a boot and sufficiently large to permit easy entrance of the foot. The latter is inserted into the machine for a distance of $8\frac{1}{2}$ inches and rests on a fine wire mesh placed about $1\frac{1}{2}$ inches from the bottom of the inner chamber. Below this platform are an electric stirrer and an electric heater. At the upper end, besides the aperture through which the foot passes, there are three other openings for a thermometer, wide glass tube, and calibrating burette, respectively (Fig. 1A: 4, 2, 3).

A cuff, made from the wrist portion of a surgical glove and connected to a diaphragm of heavy rubber (one-sixty-fourths of an inch in thickness), is attached snugly to the skin of the leg with rubber cement, and the foot is then inserted into the plethysmograph, previously two-thirds filled with water at 32° C. The upper end of the apparatus is made water-tight by stretching the membrane over the edge of the inner cylinder (Fig. 1A: 1) and clamping it in place with a brass ring. In order to prevent bulging of the rubber, a felt pad, cut out to conform to the leg, is placed above the rubber membrane and held in position with an iris diaphragm (Fig. 1B: 6). Water is added until the apparatus is filled completely, and then the thermometer, wide glass tube, and calibrating burette are placed in the three openings at the upper end of the machine (Fig. 1B: 4, 2, 3). All air is expelled and water from the burette permitted to enter until a level is observed in the glass tube. The burette is then clamped off and the glass tube connected with rubber tubing to a Brodie's bellows* of 20 c.c. capacity. A modified sphygmomanometer cuff, 2 inches wide, is placed around the leg and connected to a reservoir and mercury manometer which are so arranged that the cuff can be inflated to the desired pressure, and deflated, without any lag.

Forearm Plethysmograph.—In the case of the forearm plethysmograph, the procedure is a little more time-consuming, for, since the hand is excluded from the interior of the recording chamber, there are two openings, i.e., the entrance to, and the exit from, the apparatus, which must be made water-tight. In order to minimize vasomotor responses, it has been thought desirable to immerse the hand in water at the same temperature as that surrounding the forearm. The plethysmograph (Fig. 2), therefore, consists of an inner brass cone, the recording chamber, which is $5\frac{1}{2}$ inches long (having a diameter of $5\frac{1}{4}$ inches at one end, and $4\frac{1}{2}$ inches at the other) and contains three holes on its upper surface for the insertion of a thermometer, wide glass tube, and calibrating burette (Fig. 2B: 5, 3, 4). The inner cone is suspended permanently at its larger end in a brass receptacle (Fig. 2C). Rubber

*Recently Freeman and Zeller¹³ have suggested the use of a miniature Krogh spirometer, which evidently has certain advantages over the Brodie's bellows for recording blood flow measurements.

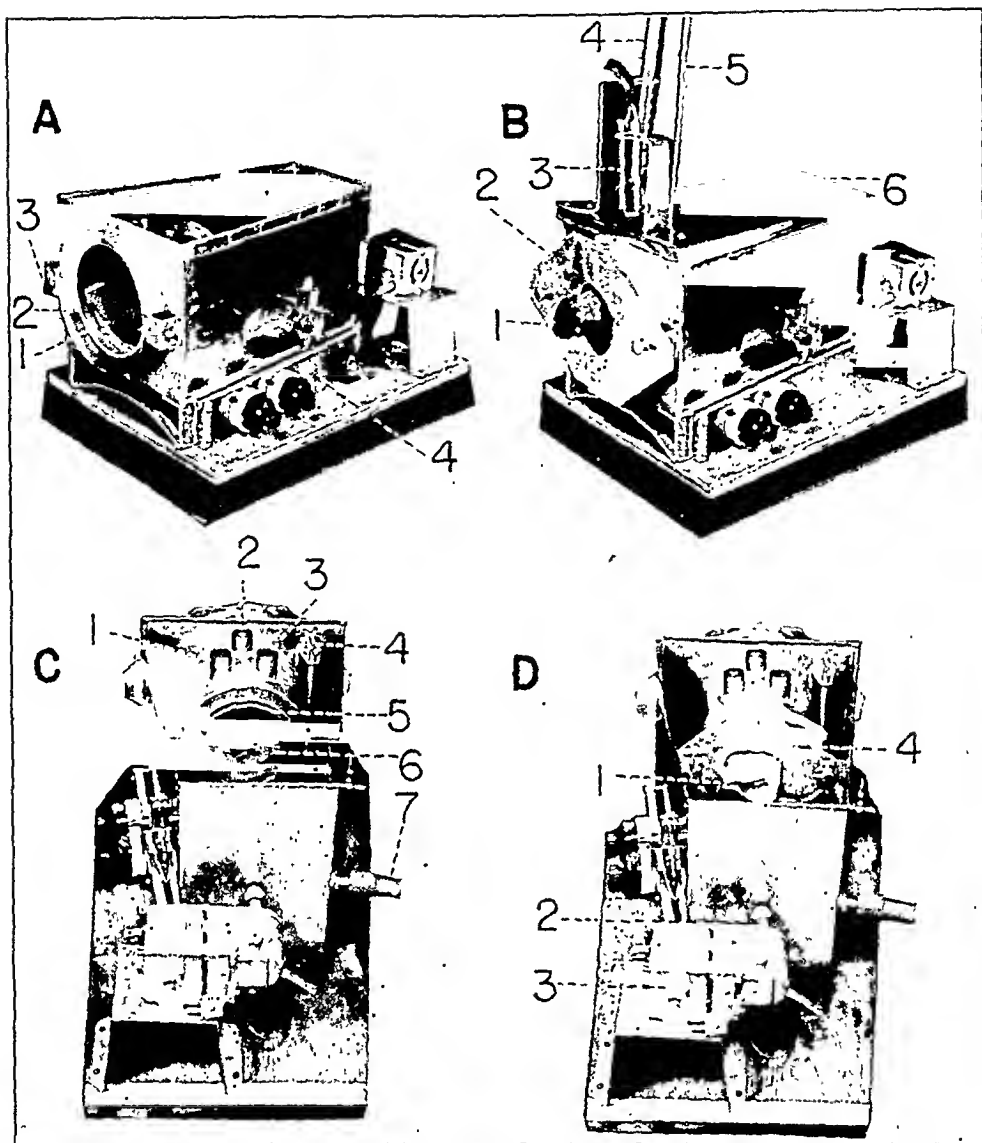


Fig. 2.—Photographs of forearm plethysmograph. *A*, View showing entrance to apparatus; 1, wire screen for support of forearm; 2, edge of inner cylinder over which rubber membrane is stretched and held in place with brass ring; 3, support for iris diaphragm; 4, panel board with switches for electric heater and propeller. Above it is a thermostat. *B*, Same view with rubber membrane stretched over ring and supported by iris diaphragm; 1, rubber cuff attached to rubber diaphragm; 2, iris diaphragm in position; 3, large glass tube; 4, calibrating burette; 5, thermometer; 6, lid covering outer chamber. *C*, View showing interior of plethysmograph; 1, opening for thermometer; 2, opening for large glass tube; 3, opening for calibrating burette; 4, outlet tube for inner chamber; 5, edge of inner cylinder over which rubber membrane is stretched and held in place with brass ring; 6, wire screen, same as *A*, 1; 7, outlet tube for outer chamber. *D*, Same view as *C* except that rubber membrane is stretched over exit to plethysmograph; 1, rubber cuff attached to rubber membrane; 2, shaft of propeller for stirring water; 3, electric motor; 4, iris diaphragm in place.

In order to convert apparatus into a hand plethysmograph, a piece of rubber sheeting is substituted for membrane with cuff attached, and this is stretched over the exit to inner chamber and supported by a wooden disc and iris diaphragm.

cuffs (each connected to a rubber diaphragm) are attached with rubber cement to the proximal and distal portions of the forearm, which is then inserted into the plethysmograph so that the hand passes through to rest on a support in the outer chamber. Both openings to the plethysmograph are made water-tight by stretching the diaphragms attached to the cuffs over the ends of the inner tube (Fig. 2A: 2 and C: 5) and retaining them in place with rings; the membranes are prevented from bulging as in the foot apparatus (Fig. 2B: 2 and D: 4). The inner and outer chambers are then filled with water at 32° C., all air is excluded from the former, and the thermometer, large glass tube, and calibrating burette are inserted into their respective openings (Fig. 2B: 5, 3, 4 and C: 1, 2, 3); the glass tube is connected by pressure tubing to a Brodie's bellows of 20 c.c. capacity. The temperature of the water in the inner and outer chambers is kept at the desired level by means of an electric heater immersed in the water, and an electric stirrer situated in the outer chamber. A lid (Fig. 2B: 6) placed over the latter diminishes the loss of heat to the outside. A blood pressure cuff, about 2 inches in width, is placed around the arm and connected to a pressure reservoir.

Hand Plethysmograph.—The forearm plethysmograph, described above, can be used to obtain blood flow in the hand alone by closing off the inner opening of the recording chamber (Fig. 2C: 5) with a piece of rubber sheeting supported by a wooden disk and iris diaphragm.* This forms a compartment large enough to contain the hand comfortably. All steps for preparing and enclosing the extremity in the plethysmograph are similar to those described above. The modified sphygmomanometer cuff (about 1½ inches wide), however, is applied to the lower portion of the forearm close to the entrance of the extremity into the plethysmograph.

The subject of the experiment lies comfortably relaxed on a couch with the extremities (generally the contralateral upper and lower ones) in their respective machines. In using the lower plethysmograph, which is raised somewhat from the floor, the thigh is slightly extended over the couch with the leg almost at right angles to the rest of the body, so as to permit the foot to rest comfortably on the wire mesh platform. Care is taken to remove any strain on the hamstrings. In using the hand or forearm plethysmograph, the upper extremity lies at about the level of the heart, making an acute angle with the trunk. The arm is supported and held firmly in place by means of sand bags, but care is taken not to exert any pressure on the superficial veins. The subject is lightly clothed and the environmental temperature is maintained as constant as possible between the limits of 25 and 27° C. All external stimuli, as well as emotional distractions, are excluded so as to reduce nervousness and apprehension to a minimum.

Since the preparations associated with the above procedures consume more than one-half hour, the subject has an opportunity to rest for at least this period of time before determinations of blood flow are made. When all preliminary work is completed, each Brodie's bellows is half filled with air and connected to a small aluminum cup-pen by a long light lever; the pens and an electric time marker, recording seconds, are then aligned on the drum. Following this, the venous pressure is measured in order to determine the degree of obstruction to the superficial veins. This is obtained by observing the lowest pressure in the cuff which causes an increase in the size of the extremity. In the hand or forearm it is generally less than 10 mm. Hg, while in the foot it is about 35 mm. Hg. Blood flow measurements are then obtained by simultaneously producing an occlusion pressure of 70 mm. Hg in the upper cuff and 110 mm. Hg in the one on the leg, maintaining it for a period of about ten seconds, and recording the initial rate of increase in the volume of each

*In some experiments the hand plethysmograph described by Freeman³ was used.

extremity. The pressures are then released and a tracing obtained of the return to the baseline. In the case of the forearm, Grant and Pearson¹² have recently presented evidence to show that it is necessary to place another blood pressure cuff around the lower portion of the extremity, close to its emergence from the plethysmograph. A pressure of 200 mm. Hg is applied fifteen seconds before, and maintained during, the period of blood flow determination. If this procedure is not followed, the rate of swelling of the portion of the forearm in the plethysmograph will be influenced by venous return from the part lying distally to it. Blood flow measurements are recorded at frequent intervals, but are never repeated within a period of time equal to twice the duration of the preceding period of application of pressure.

DISCUSSION OF METHOD

The above method may be open to criticism because of the many factors, some beyond control, which can change blood flow markedly. Therefore, in order to be able to attach significance to data thus obtained, it is essential first to present in detail the conditions under which they are collected and the precautions taken to minimize the variables.

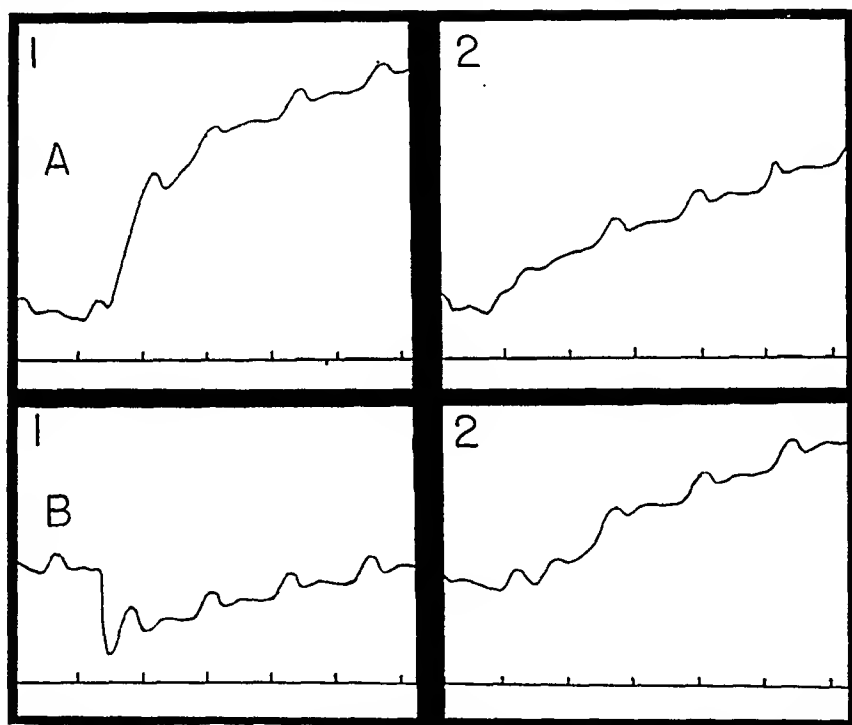


Fig. 3.—Examples of artifacts in records. A, 1, Artifact in a record representing blood flow in the foot, produced by the movement inward of the extremity upon production of occlusion pressure in the modified sphygmomanometer cuff; 2, artifact eliminated from record by readjustment of cuff. B, 1, Artifact in a record representing blood flow in the foot, produced by the movement outward of the extremity upon production of occlusion pressure; 2, artifact eliminated from record by readjustment of cuff.

Position of Sphygmomanometer Cuff.—It was found that the position of the blood pressure cuff was important in obtaining accurate readings. When applied incorrectly, it tended to produce artifacts by causing the extremity to move in or out of the plethysmograph as the pressure was let into the bag. A movement inward was easily identified by an almost

abrupt ascent of the lever and then a sudden change in the contour of the curve, which became more gradual in its rise (Fig. 3A: 1). A movement outward of the extremity generally produced a sudden drop in baseline, followed by a more gradual rise (Fig. 3B: 1). When these artifacts were observed on the drum, the position of the cuff was changed until they disappeared.

In reference to the procedure of obtaining measurements of blood flow through the hand, it was found that varying the position of the blood pressure cuff did not (except in occasional instances) alter the results so long as it remained upon the forearm. For the sake of uniformity, however, the cuff was placed around the wrist about one-half inch behind the iris diaphragm. With the forearm plethysmograph, a satisfactory position for the cuff was generally obtained by wrapping it around the lower portion of the arm, just above the elbow. In the lower extremity, it was found advantageous to place the cuff around the flattest portion of the calf, about 4 inches above the point of entrance of the leg into the plethysmograph, since the possibility of producing artifacts was less with this position than with any other one. Actually, a satisfactory application of the cuff was generally obtained only after a number of trials, and in some subjects with well-developed, bulging calf muscles it was impossible to find a position which did not result in the production of artifacts in the records.

Occlusion Pressure.—In respect to the pressures necessary to occlude veins without interfering with arterial inflow, it was found that although pressures as low as 40 mm. Hg were satisfactory for the upper extremity, with 70 mm. the effect was always maximal. Pressures above this level tended to decrease the abruptness of the ascent of the curve. In the case of the foot, it was necessary to raise the pressure to 110 mm. before consistently maximal flows were obtained, although pressures as low as 80 mm. sometimes produced similar results.

Position of Lower Plethysmograph.—As has been stated before, it was found that the constrictive effect of the glove upon the superficial veins of the upper extremity was so slight that the resulting venous pressure was generally less than 10 mm. Hg. However, in the case of the foot, although the cuff was applied with equal care, the apparent venous pressure, as measured by the method described above, was generally 35 to 40 mm. Hg. This high pressure was thought to be due to the fact that the leg was in the dependent position during the test, and also to the fact that a certain amount of the pressure applied to the leg was dissipated in compressing a greater proportion of muscle tissue (as compared with the forearm and arm) before it could effectively occlude the veins and thus increase the volume of the extremity; the latter was the criterion for determining venous pressure. In reference to the first

point, in a number of trials the lower extremity was extended horizontal to the body and the plethysmograph fitted over it in this position, whereupon it was found that practically the same minimal pressure was necessary to produce an increase in the foot-leg volume. Besides, it was soon realized that this position was impracticable, since it was conducive to the formation of leaks between the cuff and the leg because the hydrostatic pressure of the water in the plethysmograph (equal to about 25 mm. Hg) tended to peel the adherent glove away from the skin. Consequently this position was utilized only occasionally.

Air in Apparatus.—A number of previous investigators^{5, 7, 9, 13} advocated filling the plethysmograph completely with water and then removing a certain amount (10 to 50 c.c.) so that there would be a thin layer of air in the apparatus for transmission of volume changes to the Brodie's bellows. This method was tried at the beginning, but was soon found unsatisfactory for a number of reasons. First of all, there was a tendency to the formation of isolated air pockets not connected with the main body of air. These pockets acted as cushions which tended to be compressed during a blood flow determination and, as a result, the full extent of the volume change of the extremity was not recorded on the drum. Furthermore, slight movements of the hand in or out of the apparatus would vary the relative amounts of air and water present. An attempt was made to overcome this difficulty by filling the machine entirely with water before each determination, and then removing the desired amount. This was a rather tedious and time-consuming procedure and did not do away with the possibility of formation of air pockets. Another objection to the use of air in the plethysmograph was the fact that the temperature of the room was generally lower than that of the water and, as a result, the air in the plethysmograph was exposed to a temperature which was greater than that in the Brodie's bellows (which might be considered to be grossly equal to that of the room). Consequently, as the air in the plethysmograph was heated, it expanded and left the machine, and cool air replaced it, thus causing spontaneous artifacts in the baseline. This factor was especially troublesome when the temperature of the plethysmograph was raised to 45° C. while that of the room remained at 25° C.

In order to overcome the above difficulties the plethysmograph was filled entirely with water and all air pockets were dislodged by tilting the apparatus a number of times; with each attempt water was permitted to enter from the calibrating burette. When no more air could be expelled the amount of water in the plethysmograph was increased until it could be seen in the wide glass tube leading to the Brodie's bellows. It was maintained at this level throughout the experiment. In this way, only a small amount of water was exposed to the air in the recording system.

Calibration.—In most of the previous investigations with the hand plethysmograph^{5, 9, 13} the recording system was calibrated by injecting 1 to 5 c.c. of air into the tubing leading to the Brodie's bellows and then applying the scale thus obtained to determine the rate of increase of the hand volume (as represented on the drum) when the collecting pressure was applied. This method is open to criticism if absolute blood flow figures are desired, since a 1 c.c. increase in hand volume does not produce as great a rise of the lever as does an injection of 1 c.c. of air into the tubing leading to the Brodie's bellows, for the following reason: when the hand volume is increased, an equal volume of water is displaced, only part of which in turn displaces its equivalent volume of air in the recording system. The rest tends to distend or somewhat stretch the membrane through which the hand passes, even when it is supported by the felt pad and iris diaphragm. As a result, the entire volume change is not represented in the graph (for explanation see below). Furthermore, since the tension of the rubber membrane will most likely be different in each experiment (resulting in variations in the sensitivity of the apparatus), while the calibration with the above method will always remain constant, another source of error may be introduced if comparisons of absolute blood flow determinations are made under these conditions. However, for any experiment which is complete in one trial, relative figures will have some significance.

In the present investigation calibrations were made under conditions similar to those of the blood flow measurements. In other words, each plethysmograph was calibrated with the extremity in place by permitting water from the burette to enter the machine in 2 c.c. amounts and recording the rise of the lever with each increment. In the case of the hand, since oscillations resulting from the heart beat as well as spontaneous variations in vasomotor tonus tended at times to introduce a large error, a pressure of 200 mm. Hg was generally introduced into a cuff on the arm during the period of calibration in order to obstruct all flow of blood into the extremity. In the case of the foot or forearm, such precautions were generally not necessary because spontaneous changes in the baseline were not marked. The calibrations thus obtained were used as a basis for forming a scale in which each subdivision was equal to 0.25 c.c.; the sensitivity of the recording system was such that the lever of the bellows rose about 15 mm. on the drum with each volume change of 1 c.c. in the plethysmograph. By means of this scale the rate of peripheral blood flow was calculated by measuring the height of average rise from the baseline of each curve at the end of the first second following the application of the collecting pressure. The initial portion of the tracing was the most rapid in its ascent and consequently

more nearly represents unopposed arterial inflow. All tracings which curved upward for a short period of time (one second, or so) and then flattened out to form a plateau were discarded because they most likely indicated the presence of an abnormally large quantity of blood in the venules and veins. This would tend to oppose the flow of blood into the extremity and hence contribute toward low blood flow determinations. The figures obtained from records considered satisfactory were then converted into flow per minute and flow per minute per 100 c.c. of limb volume. The volume of the hand or forearm was readily obtained by subtracting the amount of water necessary to fill the plethysmograph with the extremity in place from the figures representing the capacity of the apparatus. The foot-leg volume was obtained by inserting that part of the extremity previously in the plethysmograph into a large container completely filled with water and measuring the displacement volume. Generally, the hand volume varied from 350 to 550 c.c., the forearm from 400 to 600 c.c., and the foot-leg volume from 1200 to 1800 c.c.

Diameter of Glass Tube of Recording System.—The fact that a large glass tube was used in each plethysmograph to join the rubber tubing connected with the Brodie's bellows to the apparatus has been purposely stressed, for it was found that when a small tube (about 0.5 cm. in diameter) was substituted for the one in the hand or forearm plethysmograph (2.2 cm. in diameter) the sensitivity of the recording system was markedly diminished. For example, the entrance of 2 c.c. of water from the calibrating burette into the hand or forearm plethysmograph generally caused the lever (of a constant length) connected to the Brodie's bellows to rise about 30 mm. with the larger tube in place, but this response was diminished to 9 mm. with the smaller tube. In fact, if a narrow tube was utilized with the foot plethysmograph, the sensitivity of the entire system was so slight as to make it almost impracticable for use. The cause for this difference in response is partly the same as that which accounts for the marked variations between water and air calibrations. For, as has been stressed, the plethysmograph is not a chamber of fixed capacity, since it has one wall (in the case of the forearm, two walls) composed of rubber membrane which remains distensible. Consequently, during a blood flow determination, when a rise in the height of the column of water in the glass tube takes place there is an increase in the hydrostatic pressure of the system, which in turn further stretches the membrane. As is obvious, the entrance of equal quantities of water into a large and a small tube, respectively, will result in a much greater increase in hydrostatic pressure in the latter, and hence produce a greater distention of the membrane, with a less marked effect upon the recording system.

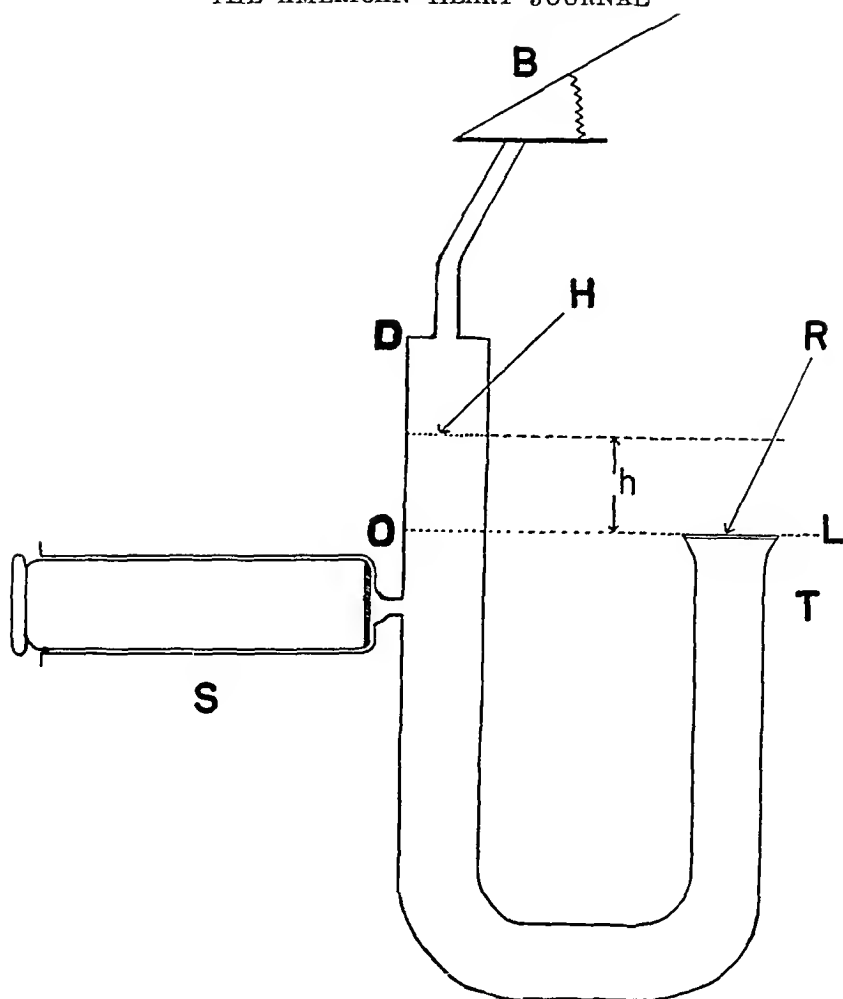


Fig. 4.—See text for explanation.

The explanation for the above findings can be presented more simply by means of a substitute system (Fig. 4) which has all the essential physical properties of the plethysmograph and its recording mechanism. The plethysmograph itself is represented by the U tube, *T*, one limb of which is covered at its upper end by a rubber membrane, *R*, the equivalent of the elastic pocket formed by the rubber diaphragm of the plethysmograph. The syringe, *S*, is utilized to deliver a definite volume of water to the apparatus, imitating the swelling of the extremity during a blood flow determination. *OD* is the equivalent of the tube leading to the Brodie's bellows from the plethysmograph. The water level, *H*, in this tube acts like a piston to displace a volume of air which in turn raises the Brodie's bellows, *B*, with its attached lever. Now, if a rigid membrane is substituted for the rubber one, *R*, then the addition of a definite volume of water to the U tube (previously filled with water to the level, *L*) will cause the water to rise a certain height, *h*, in *OD*. If the rubber membrane is now replaced and the same step performed, the rise in *OD* will be greater than $\frac{h}{2}$ but less than *h* for the following reason:

The rubber membrane will be exposed to a force which tends to distend it, thus increasing the volume capacity of the space bordered by the membrane. The magnitude of this force is determined by the difference in height of the points *H* and *R*, equal to *h*; the larger *h* is for a given injected volume, the greater is the force, and hence the elastic loss. The greater the diameter of *OD*, the smaller is *h* for the same injected volume. Therefore, it follows that the loss will become less and less, as the cross section of *OD* increases.*

*We are indebted to Dr. A. Kolin of Mt. Sinai Hospital for the above explanation.

By applying the various plethysmographs to the limbs as described above, blood flow determinations which are representative of different combinations of peripheral blood beds can be obtained. For instance, in the case of the hand, the predominant flow is through the skin and subcutaneous tissues, which, according to Grant and Pearson,¹² make up about 50 per cent of the volume of the fingers. On the other hand, figures obtained for the upper portion of the forearm will indicate largely the flow through muscle, since about 85 per cent of the volume is made up of this tissue.¹² Finally, in the case of the lower extremity, with all of the foot and part of the leg in the plethysmograph, a composite type of response will be elicited.

By obtaining blood flow measurements in a foot and hand, or a foot and forearm, a means is at hand for determining simultaneously the effect of various physiologic procedures upon the different types of blood beds. Further, by varying conditions to which one extremity is exposed, distant effects on blood flow can be observed as manifested by changes in the other.

SUMMARY

The various pitfalls associated with plethysmographic determinations of blood flow in the extremities are presented. The criteria used to recognize and eliminate artifacts in the records are discussed.

REFERENCES

1. Stewart, G. N.: Studies on the Circulation in Man. I. The Measurement of the Blood Flow in the Hands. II. The Effect of Reflex Vasomotor Excitation on the Blood Flow in the Hands, *Heart* 3: 33, 1911.
Stewart, G. N.: Studies on the Circulation in Man. The Blood Flow in the Hands and Feet in Normal and Pathological Cases, *The Harvey Lectures* 8: 86, 1912-1913.
2. Pickering, G. W.: Observations on the Mechanism of Arterial Hypertension in Acute Nephritis, *Clin. Sc.* 2: 363, 1936.
3. Brodie, T. G.: Gas Metabolism of Small Intestine During the Reabsorption of Witte's Peptone, Seventh International Physiological Congress, August, 1907.
4. Hewlett, A. W., and van Zwaluwenburg, J. G.: The Rate of Blood Flow in the Arm, *Heart* 1: 87, 1909-10.
5. Freeman, N. E.: The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, *Am. J. Physiol.* 113: 384, 1935.
6. Killian, J. A., and Oclassen, C. A.: Comparative Effects of Water Baths and Mustard Baths at Varying Temperatures on the Rate of Peripheral Blood Flow in Man, *AM. HEART J.* 15: 425, 1938.
7. Lampson, R. S.: Quantitative Study of Vasoconstriction Induced by Smoking, *J. A. M. A.* 104: 1963, 1935.
8. Wilkins, R. W., Weiss, S., and Haynes, F. W.: The Effect of Epinephrin in Circulatory Collapse Induced by Sodium Nitrite, *J. Clin. Investigation* 17: 41, 1938.
9. Capps, R. B.: Method for Measuring Tone and Reflex Constriction of Capillaries, Venules and Veins of Human Hand With Results in Normal and Diseased States, *J. Clin. Investigation* 15: 229, 1936.
10. Lewis, T., and Grant, R. T.: Observations Upon Reactive Hyperaemia in Man, *Heart* 12: 73, 1925-26.
11. Prinzmetal, M., and Wilson, C.: Nature of Peripheral Resistance in Arterial Hypertension With Special Reference to Vasomotor System, *J. Clin. Investigation* 15: 63, 1936.
12. Grant, R. T., and Pearson, R. S. B.: The Blood Circulation in the Human Limb: Observations on the Differences Between the Proximal and Distal Parts and Remarks on the Regulation of Body Temperature, *Clin. Sc.* 3: 119, 1938.
13. Freeman, N. E., and Zeller, J. W.: The Effect of Temperature on the Volume Flow of Blood Through the Sympathectomized Paw of the Dog With Observations on the Oxygen Content and Capacity, Carbon-Dioxide Content, and the pH of the Arterial and Venous Blood, *Am. J. Physiol.* 120: 475, 1937.

PLETHYSMOGRAPHIC STUDIES OF PERIPHERAL BLOOD FLOW IN MAN

II. PHYSIOLOGIC FACTORS AFFECTING RESTING BLOOD FLOW IN THE EXTREMITIES*

DAVID I. ABRAMSON, M.D.,† HERMAN ZAZEELA, M.D., AND
JOSEPH MARRUS, B.S.
CINCINNATI, OHIO

IN A preceding paper¹ attention was called to the mechanical and physical difficulties in the use of the plethysmograph which might lead to erroneous determinations of blood flow measurements in the extremities. In addition to these, there are numerous physiologic factors which may also produce marked variations. In the present report these are described and means of control or elimination suggested, in order that significant and reproducible data may be obtained. As reported in the previous paper,¹ the foot plethysmograph was used in conjunction with either a forearm or hand apparatus.

1. *Spontaneous Variation in Vasomotor Tonus*.—One of the most important factors contributing to variations in blood flow is the spontaneous changes in vasomotor tonus occurring during the period of observation. This is especially so in the case of the hand, which, because of its relatively large area of highly specialized skin with many arteriovenous shunts, is particularly responsive to impulses from the vasomotor center. In order to minimize this extraneous influence, blood flow measurements were made with the blood vessels in the hand relatively dilated. This state was determined when the baseline of the recording system spontaneously reached its highest level, indicating a maximal blood volume in the extremity as a result of more rapid blood flow through it per unit of time. Once this level was observed, it was used throughout the experiment. Possible errors arising from spontaneous variations were further obviated by recording at least thirteen to fifteen consecutive resting blood flow measurements and computing the average of the figures. In the case of the foot and forearm these difficulties are not encountered to the same extent.

2. *Effect of Painful Stimuli*.—Fluctuations such as are observed during the period when the skin is being prepared for insertion of a needle into a vein, or during the actual procedure of injection, cannot be entirely eliminated, but they may be obviated somewhat by using subjects who are stolid and have previously been exposed to many similar tests.

*From the Medical Service of B. S. Oppenheimer, Mt. Sinai Hospital, New York, and the Institute for Medical Research, The Jewish Hospital, Cincinnati, Ohio.

Aided in part by the Samuel and Regina Kuhn Fund.

†Work done in part during tenure of the Richard and Ella Hunt Sutro Fellowship.
Received for publication Aug. 8, 1938.

Since painful stimuli generally produce vasoconstriction,² a decrease in blood flow during these periods is given little consideration in the interpretation of the data.

3. *Effect of Varying Temperature of Water in Plethysmographs (Bath Temperature).*—A. Flow at 32° C. Since it was found that exposing the extremity in the plethysmograph to the low bath temperature (20 to 25° C.) used in some studies produced a marked slowing of blood flow, it was decided to adopt more nearly physiologic conditions by maintaining the temperature of the water at the same level as that of the skin, namely, at 32° C. Examination of Table I reveals that the average flow per minute per 100 c.c. of limb under these conditions is greatest in the hand, less in the foot (including the lower portion of the leg) and least in the forearm (Fig. 1). In some instances, following the above

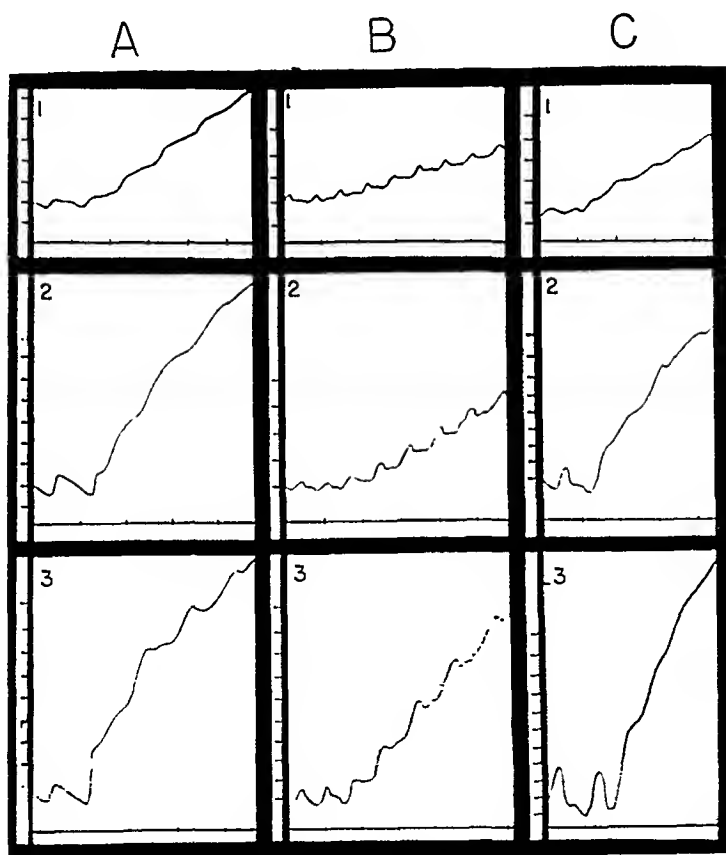


Fig. 1.—Effect of varying bath temperature in plethysmographs upon blood flow in hand, forearm, and foot (with portion of leg). Subject L. S.

	(1) FLOW AT 32°C. (C.C.)	(2) FLOW AT 32°C. WITH VESSELS REFLEXLY DILATED (C.C.)	(3) FLOW AT 45°C. (C.C.)
A, right hand (vol. 430 c.c.)	10.6	27.3	33.0
B, right forearm (vol. 600 c.c.)	2.5	4.7	11.1
C, left foot (vol. 1450 c.c.)	4.9	10.1	15.2

All figures represent the number of cubic centimeters of blood flow per minute per 100 c.c. of limb volume. Time in seconds. Calibrations, 1 division equals 0.5 c.c.

step reflex vasodilatation of one or both extremities in the plethysmographs was then produced by applying heat to other portions of the body for at least three-quarters of an hour.^{3, 4} Generally, an increase in blood flow was obtained which was especially marked in the hand and less so in the forearm and foot (Fig. 1), which observations are in accord with those of Grant and Pearson.⁵ In the case of four subjects on whom paravertebral block had been performed previously, this phenomenon was not elicited in the anesthetized foot. These findings in the lower extremity are further confirmatory evidence for the statement that reflex vasodilatation depends upon the integrity of vasomotor nerves, a view which is based upon observations in the normal and sympathectomized hand.^{3, 6, 7}

TABLE I

RESTING BLOOD FLOW MEASUREMENTS AT BATH TEMPERATURES OF 32° AND 45° C. AND ROOM TEMPERATURE BETWEEN 25° AND 27° C.

SUBJECT	AGE	HAND			FOREARM			FOOT-LEG		
		NO. OF TRIALS	FLOW AT 32°	FLOW AT 45°	NO. OF TRIALS	FLOW AT 32°	FLOW AT 45°	NO. OF TRIALS	FLOW AT 32°	FLOW AT 45°
K. M.	24				3	2.4	7.2	1	5.4	13.9
L. S.	50	4	14.8	33.2	3	2.3	12.8	12	4.2	15.0
V. B.	29				2	1.7	6.8	1	4.0	
R. T.	23				2	2.3	11.8			
N. G.	22				3	1.8	7.1	1	5.0	
D. G.	21				2	3.1	7.8	1	3.0	
J. M.	28	2	10.3	39.0				1	1.3	9.9
F. A.	30							1	2.4	17.2
S. S.	42	6	21.9	39.2						
L. N.	2	2	19.1	38.3				1	6.6	10.5
R. W.	19							1	3.6	
A. S.	23							1		15.6
P. S.								1	4.7	
L. K.		2	19.1	35.5				2	3.3	14.9
A. B.	44	8	10.5	41.0				9	3.9	
J. G.	22	2	11.0					1	5.8	
M. S.	26	4	11.2							
J. T.	41	2	10.0							
E. R.	36	2	15.0	37.5						
H. F.		7	16.9	39.6						
P. M.	50	7	19.7	34.7						
S. N.	38	3	18.1	34.1						
R. G.	27	2	10.1	40.5						
F. A.		2	13.0	39.8						
F. S.		1	12.2	41.9						
H. L.	38	8	11.5	33.1						
S. R.	33	4	9.1	37.1						

All figures represent blood flow per minute per 100 c.c. limb volume.

B. Flow at 45° C. When the flow at 45° C. is compared for the three sites (Table I), that in the hand is uniformly greater than that in either the foot or forearm; this difference is probably due to the greater quantity of blood flowing through the specialized skin vessels of the fingers. As noted in Table I, the range of normal blood flow measurements in the hand varies to a much greater extent when the bath temperature is 32° than when it is 45° C. This may be ascribed to the

probability that fluctuations in vasomotor tonus are more apparent at the lower temperature. Further evidence for this view is the fact that spontaneous variations in the baseline generally observed at 32° are practically absent at 45°.

4. *Effect of Varying Environmental Conditions.*—Other factors which must be controlled in order to obtain comparable blood flow readings are the relative humidity (which should be around 50 per cent) and the temperature of the room. The most satisfactory range for the latter for obtaining stable results is between 25 and 27° C., for under these conditions there is neither marked peripheral vasoconstriction nor dilatation. If the temperature drops a degree or more below the lower limits, the resting flow at a bath temperature of 32° is significantly diminished, or if it rises much above 27° the flow tends to approach in magnitude that obtained with reflex vasodilatation. In certain respects these last two states (i.e., flow at high room temperatures and that with reflex vasodilatation) are similar, one merely representing a somewhat more marked stage of the other.

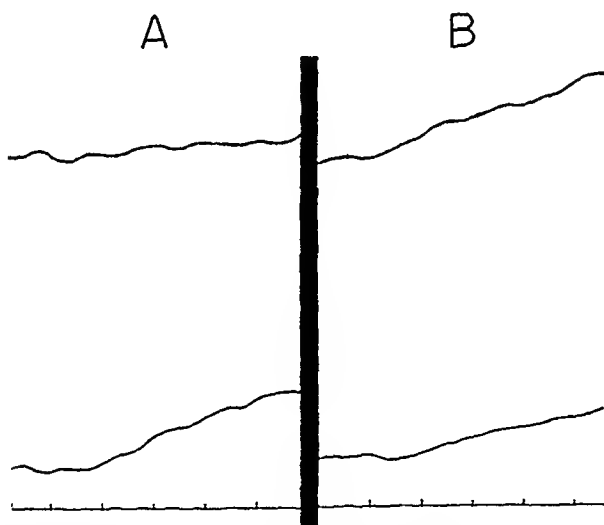


Fig. 2.—Effect of varying environmental temperature upon blood flow in a subject (H.L.) abnormally sensitive to cold. A, Room temperature of 21 to 24°. Upper graph, flow in right hand (vol. 480 c.c.) 4.6 c.c. Lower graph, flow in left foot and adjoining portion of leg (vol. 1300 c.c.) 3.1 c.c. B, Room temperature of 25 to 27°. Upper graph, flow in right hand (vol. 450 c.c.) 12 c.c. Lower graph, flow in left foot and portion of leg (vol. 1350 c.c.) 2.6 c.c. Time in seconds. Bath temperature 32°.

An exaggerated example of the effect of lowering room temperature on blood flow is demonstrated by the responses of a subject (H.L.) who reacted markedly to cold (Fig. 2-B). In the case of the right hand, the average resting blood flow was 4.6 c.e. per minute per 100 c.e. of limb when the temperature of the room varied between 21° and 24°, and 12 c.e. at a range between 25° and 27° C. (average of six experiments for each range of temperature). Likewise, in the left hand, it was 3.9 c.e. (average of four experiments) at the lower room temperature, and 11.1 c.e. (average of five experiments) at the higher level. The differ-

ences in the feet were not as marked, which may have been due partly to the presence of a paravertebral block on both sides. In the right foot the flow was 2.5 c.c. (average of four experiments) at the lower, and 3.4 c.c. (average of five experiments) at the higher ranges, while in the left it was 1 c.c. (average of two experiments) and 3.6 c.c. (average of six experiments) at the lower and higher temperatures, respectively. In every instance the portion of the extremity in the plethysmograph was exposed to water at a constant temperature of 32° C., but evidently the flow through it was affected by raising or lowering the temperature of the air surrounding the rest of the body. When the bath temperature was raised to 45°, however, there was no significant difference between the figures obtained at the high and low room temperatures. This was so in the case of all the sites studied. In other words, vasomotor changes resulting from variations in environmental conditions are ineffective in the presence of the strong vasodilatation produced by the direct application of heat. At this point, therefore, it must be emphasized that many variables can modify blood flow measurements of the hand, at least at a bath temperature of 32° (the one frequently employed in plethysmographic studies); on the other hand, at 45° the determinations are less affected by extraneous factors and hence indicate more accurately the actual state of the peripheral circulation.

5. *Local Reflex Effect Elicited by Application of Occlusion Pressure to Lower Extremity.*—It was noticed during the preliminary work of obtaining measurements in the lower extremity at 32° that after the release of the occlusion pressure the lever quickly fell to the level of the previous baseline, and then dropped much below, to return slowly. This finding, indicating a decrease in limb volume, was generally present in foot records of many normal subjects (Fig. 3) and was occasionally observed in the hand as well. In order to investigate the matter, gradually decreasing pressures were applied to the leg until a level finally was reached which produced no increase in the foot-leg volume, i.e., was not sufficient to cause any obvious venous occlusion. However, even under these circumstances releasing the pressure resulted in the drop below the baseline (equivalent to a decrease of 0.5 to 2 c.c. of limb volume) and a return in from fifteen seconds to two minutes (Fig. 4). Occasionally a rise above the baseline followed the drop. The degree of response could not be correlated with either the height of the pressure or the previous duration of application of this pressure.

This phenomenon was then studied in a series of four patients in whom paravertebral block of the lower extremities had been produced previously. In each instance, upon application of the occlusion pressure to the anesthetized leg the same reflex was elicited (Fig. 3, 2). On the other hand, when the temperature of the water in the foot plethysmograph was raised to 45°, in these patients as well as in normal subjects, the momentary drop in foot volume was no longer observed (Fig. 3, 3).

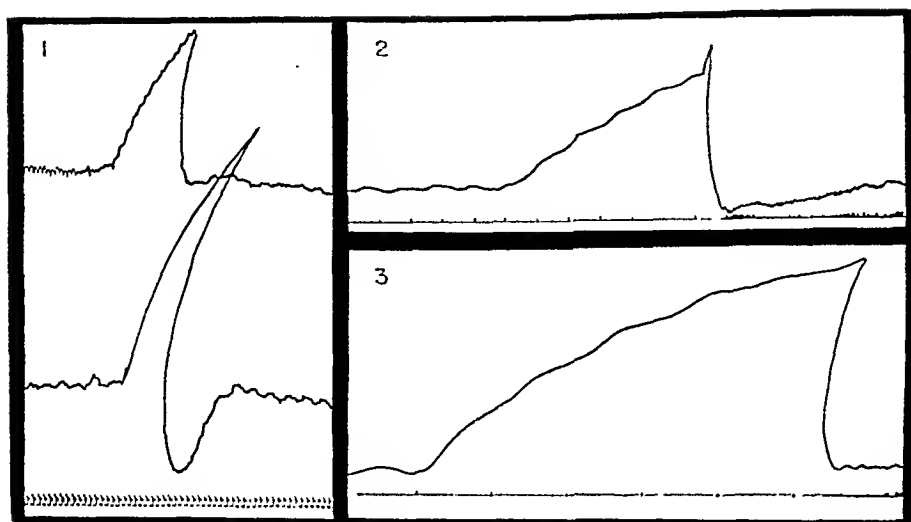


Fig. 3.—Effect produced by the application of occlusion pressure. 1, Upper graph, flow in hand following application of occlusion pressure of 70 mm. Hg to wrist for nine seconds. No drop in baseline below previous level on release of pressure. Lower graph, flow in foot following application of occlusion pressure of 110 mm. Hg. Definite drop in baseline below previous level on release of pressure and then a gradual return. 2, Application of occlusion pressure of 110 mm. Hg to right leg (paravertebral block produced two months previously). Definite drop in baseline below previous level on release of pressure and then a gradual return. All readings obtained at bath temperature of 32°. 3, Application of occlusion pressure of 110 mm. Hg to leg with the bath temperature at 45°. No drop in baseline below previous level on release of pressure. Time in seconds.

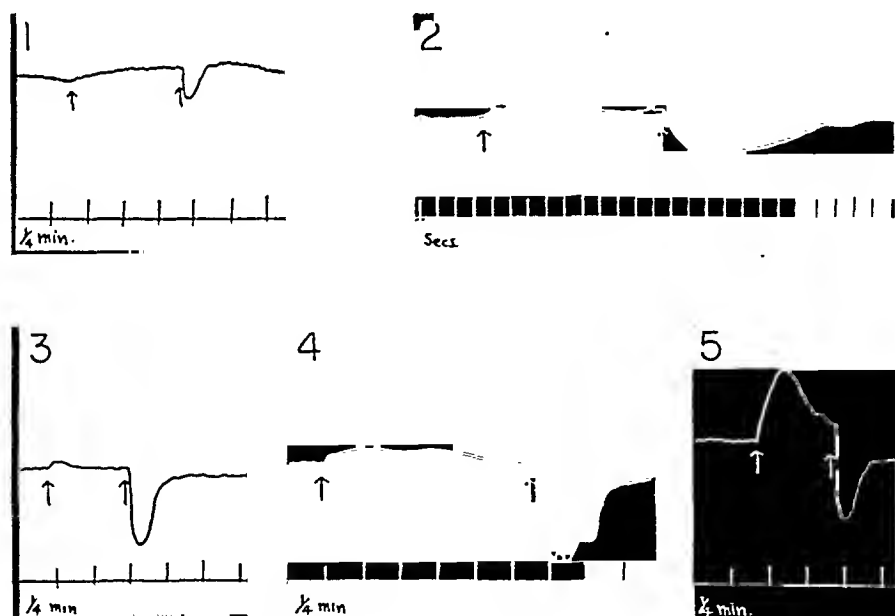


Fig. 4.—Effect produced by the application of different amounts of pressure to the leg (in which paravertebral block had been produced previously). Bath temperature, 32°. Duration of pressure indicated by arrows. 1, Application of 30 mm. Hg; 2, application of 35 mm. Hg; 3, application of 40 mm. Hg; 4, application of 45 mm. Hg; 5, application of 50 mm. Hg.

In every instance a drop in baseline (denoting a decrease in volume of the extremity) is noted upon release of the pressure. In record 1 a rise above the baseline follows the drop.

This response, therefore, is probably due to vasoconstriction of the blood vessels in the foot as a result of the elicitation of some local reflex.* Whether the effect is upon the arteriolar or the venous bed has not been determined. That it is not due to passive drainage of blood away from the leg is supported by the fact that the extremity is in a dependent position, which would oppose such a tendency. Since the reaction can be produced by the application of a pressure so low that no change in the volume of the foot is observed, it does not seem reasonable to assume that the provoking mechanism is stretching of the vessel wall by an increased intravascular pressure. Comparison of this response with that resulting from a pinch of the skin, as described by Capps,⁹ reveals certain differences between the two. For, whereas in the latter procedure vasoconstriction is obtained immediately upon the application of the painful stimulus to the arm, in the former the response is observed upon removal of the pressure, and then generally only in the case of the foot. It is of interest that the volume change produced by the pressure is abolished by local heat. Evidently the exaggerated vasodilatation resulting from the latter procedures is sufficient to overcome any vasoconstriction produced reflexly. These findings are further proof for the belief that blood flow determinations obtained at a bath temperature of 45° C. are more stable and more significant than those obtained at other temperatures.

6. *Effect of Increase in Local Venous Pressure.*—In a patient, A. G., suffering from carcinoma of the lung and metastasis to the lymph nodes of the right axilla, an opportunity was offered to observe the local effect of increased venous pressure upon blood flow in an extremity. The enlarged lymph nodes were evidently producing pressure upon the veins and causing a discernible swelling of the skin and subcutaneous tissue of the right arm. The venous pressure was 190 mm. of water in this extremity as compared with 120 mm. in the left, while the arterial pressure was the same in both. Blood flow measurements in the hands were obtained on three different occasions, the order with which they were recorded being changed each time. In every instance, the blood flow in the right hand was definitely and significantly greater than that in the left; the average for the former was 12.9 c.c. per min. per 100 c.c. of limb as compared with 7.3 c.c. for the latter (Fig. 5).

The fact that blood flow may be increased in an extremity in which the venous pressure is high may possibly be explained on the following basis: A rise of pressure within the veins and venules causes them to become distended because of the looseness of the tissues supporting

*This finding may be of more than academic interest in respect to the widely used method of intermittent venous occlusion⁸ in the treatment of peripheral vascular disease of the lower extremities. That a reflex which produces vasoconstriction is elicited by a procedure grossly similar to that utilized in the method suggests that the physiologic rationale for this treatment should be subjected to further investigation.

them. As a result, there is stasis of blood in these vessels (since for equal quantities of blood flowing into the veins the velocity will be inversely proportional to cross-sectional area) with consequent anoxemia of the tissues. Possibly then, in response to stasis and tissue anoxemia, a state comparable to reactive hyperemia¹⁰ is brought about, which in turn affects the caliber of the terminal arterioles and thus causes a compensatory increase in local arterial blood flow.

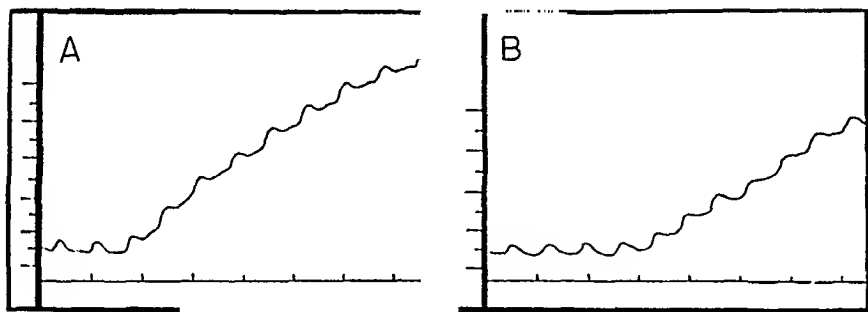


Fig. 5.—Effect of increased venous pressure upon blood flow. Subject (A.G.) with carcinoma and metastasis to lymph nodes in the right axilla producing increased venous pressure in right upper extremity. A, Blood flow in right hand (vol. 550 c.c.) 14.4 c.c. Venous pressure, 190 mm. water. B, Blood flow in left hand (vol. 550 c.c.) 7.1 c.c. Venous pressure, 120 mm. water.

7. *Variations in Blood Pressure.*—We were fortunate to have at our disposal a woman patient, aged 26, who was found to have a brachial blood pressure ranging between 160 and 230 mm. Hg systolic and 120 and 130 mm. Hg diastolic in the right arm, and between 120 and 130 mm. Hg systolic in the left arm; the diastolic level was difficult to obtain in the left arm. The cause for this phenomenon could not be ascertained with certainty, although the possibility of a generalized hypertension with some obstruction to the flow in the left arm was entertained, since the pressure in the legs was also elevated. There was no apparent difference in the color of the skin or the size and muscular development of the two arms, although the pulse was much more difficult to palpate in the left and there was a discernible delay in its arrival. Nevertheless, the blood flow in the two hands was identical [i.e., within the range of experimental error (Fig. 6)], a finding which was anticipated in view of the similarity in the size and appearance of the two extremities. Measurements were then obtained after the application of a pressure of 200 mm. Hg to each arm separately for ten minutes in order to produce reactive hyperemia (Fig. 6). In the left hand the greatest flow after release of pressure was 19.4 c.c. per minute per 100 c.c. of hand (average resting flow 4.8), whereas in the right it was 30 c.c. (average resting flow 5.4); i.e., the flow in the right was 50 per cent greater than in the left under these conditions. The results obtained during reactive hyperemia suggest either a constantly existing state of exaggerated vasoconstriction of the blood vessels in the right hand,

or more probably a compensatory vasodilatation in those of the left hand. As a result, blood flow through each extremity per unit of time was the same despite marked differences in blood pressure. This case demonstrates to a certain degree the influence of one type of abnormality of the blood vessels upon blood flow in the extremities.

8. *Ingestion of Food.*—In view of the well-known effect of the ingestion of food upon cardiac output, an attempt was made to keep this factor as constant as possible by beginning all experiments about the same time after the last meal (two and one-half hours).

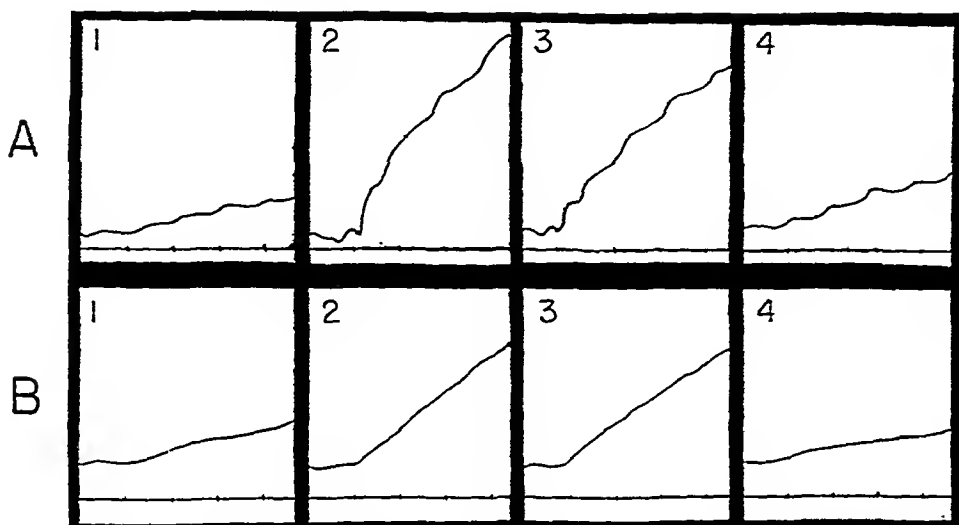


Fig. 6.—Effect of different levels of systolic blood pressure upon resting blood flow and flow after reactive hyperemia (subject R. B.). Blood pressure in right arm $\frac{210}{140}$, and in the left $\frac{130}{70}$. Bath temperature, 32°. A, Blood flow in the right hand (vol. 400 c.c.). 1, Resting blood flow, 5.4 c.c. Records 2, 3, and 4 obtained at 30 seconds (flow, 30 c.c.), 70 seconds (flow, 22.5 c.c.), and 190 seconds (flow, 7.5 c.c.), after removal of a pressure of 200 mm. Hg applied to the right arm for ten minutes in order to produce reactive hyperemia. B, Blood flow in the left hand (vol. 350 c.c.). 1, Resting flow, 4.8 c.c. Records 2, 3, and 4 obtained at 30 seconds (flow 19.4 c.c.), 70 seconds (flow 14.5 c.c.) and 190 seconds (flow 4.8 c.c.), after production of reactive hyperemia as in A. Time in seconds.

9. *Sleep.*—Another factor which it was found necessary to control was the state of consciousness of the subject. Dozing or actual sleep in some instances produced a decrease in blood flow, especially in the upper extremities (Fig. 7); this drop was even more accentuated by sudden awakening. Further evidence for the presence of a diminished flow was a concomitant drop in the level of the baseline (indicating a smaller limb volume) and a flattening out of the oscillations normally present in the records (Fig. 7).

10. *Shock.*—As has been reported,^{2, 11} in the presence of shock the blood flow to the periphery is markedly reduced. In circulatory collapse induced by sodium nitrite¹¹ the responsible mechanism is a pooling of blood in the venules and veins (resulting in reduced venous return and hence diminished cardiac output) coincident with reflex arteriolar constriction. These factors also play a role in surgical shock. During the course of a study on the influence of vasodilator drugs, we

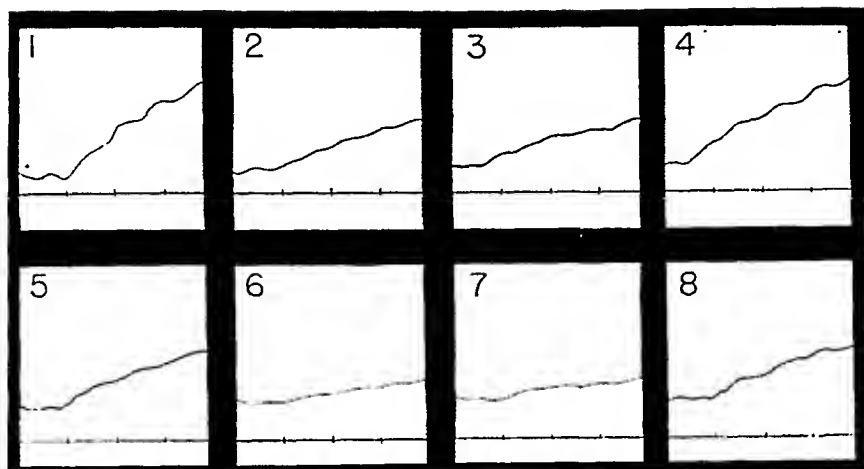


Fig. 7.—Effect of sleep upon blood flow in the left hand (subject A. K.). Bath temperature, 32°. 1, Resting blood flow (vol. 465 c.c.) 12.4 c.c. Records 2 to 7, inclusive, taken during period in which subject was asleep. 2, Blood flow, 6.5 c.c.; 3, blood flow, 5.8 c.c.; 4, blood flow, 9.8 c.c.; 5, blood flow, 6.5 c.c.; 6, blood flow, 2.6 c.c.; 7, blood flow, 3.2 c.c.; 8, taken after patient was awakened, blood flow, 7.9 c.c. Time in seconds.

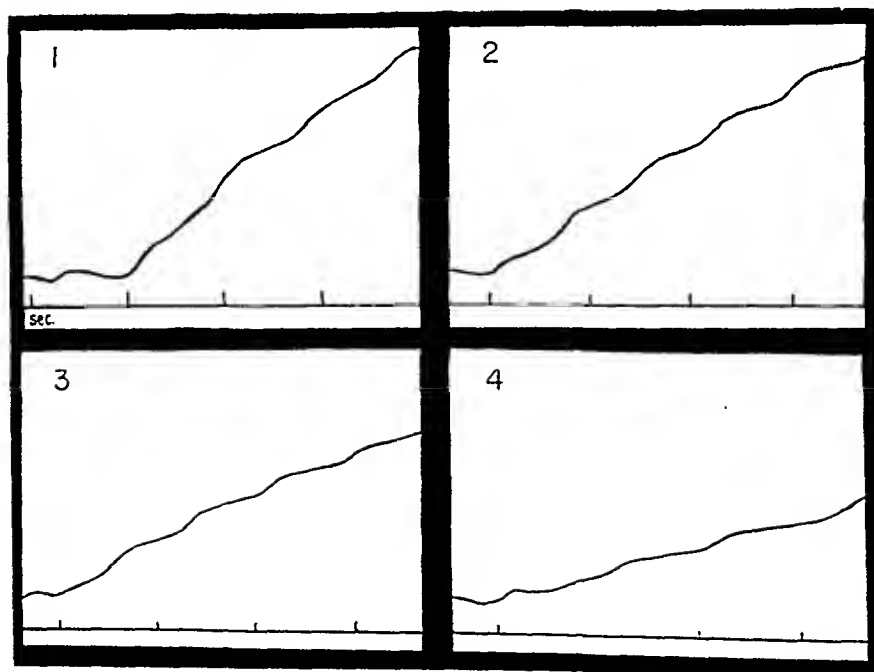


Fig. 8.—Effect of diminished cardiac output (as a result of shock) upon peripheral blood flow (subject H. L.). Blood flow in right foot (vol. 1450 c.c.). Bath temperature, 45°. 1, Control blood flow, 11.3 c.c. Records 2, 3, and 4 taken at varying intervals after onset of symptoms of shock. 2, Five minutes after, 7.4 c.c.; 3, seven minutes after, 7.7 c.c.; 4, twenty-four minutes after, 3.3 c.c. Time in seconds.

had the occasion to observe a subject who went into shock as a result of a slightly different mechanism. In this individual, H. L., two extremities in plethysmographs were exposed to a bath temperature of 45° C. for about one hour, and then 1 c.c. of "spasmalgin" (combination of atropine, pantopon, and papaverin) was injected intravenously. Immediately upon the completion of this procedure, the patient began to complain of weakness and palpitation, became pale, and the blood pressure fell. During this period blood flow in the lower extremity was definitely reduced (Fig. 8). The decreased peripheral flow in this instance was evidently due to a diminished venous return, resulting from the marked vasodilatation produced both by the heat and the drug. It is improbable that any effective vasoconstriction could occur in the extremities in the plethysmographs because of the counteracting local vasodilatation. Indirect evidence for this view is the fact that the oscillations in the blood flow records, which are coincident with the heart beat, were only slightly changed in amplitude during the period of diminished flow; for these oscillations are primarily influenced by alterations in caliber of blood vessels and to a much lesser degree by cardiac output. This experience, therefore, emphasizes the effect of changes in cardiac output upon peripheral circulation. As is obvious, this factor is as important as the state of the blood vessels in determining the resultant rate of blood flow.

SUMMARY

The various physiologic factors which may modify normal resting blood flow determinations are discussed, and methods for obviating them are presented.

The normal ranges of blood flow values for the hand, forearm, and foot under different states of vasomotor control are presented and their significance discussed.

A local reflex is described which produces vasoconstriction of the blood vessels of the lower extremity on release of the occlusion pressure used in obtaining blood flow figures.

The authors wish to express their appreciation to Dr. Mae Friedlander for help in carrying out the preliminary experiments, and to Dr. S. Silbert, who was instrumental in supplying them with many of the patients studied and contributed numerous helpful suggestions.

REFERENCES

1. Abramson, D. I., Zazeela, H., and Marrus, J.: Plethysmographic Studies on Peripheral Blood Flow in Man. I. Criteria for Obtaining Accurate Plethysmographic Data, *AM. HEART J.* 17: 194, 1939.
2. Freeman, N. E., Shaw, J. L., and Snyder, J. C.: Peripheral Blood Flow in Surgical Shock; Reduction in Circulation Through Hand Resulting From Pain, Fear, Cold, and Asphyxia, With Quantitative Measurements of Volume Flow of Blood in Clinical Cases of Surgical Shock, *J. Clin. Investigation* 15: 651, 1936.
3. Lewis, T., and Landis, E. M.: Some Physiological Effects of Sympathetic Ganglionectomy in the Human Being and Its Effect in a Case of Raynaud's Malady, *Heart* 15: 151, 1929-31.

4. Gibbon, J. H., and Landis, E. M.: Vasodilatation in Lower Extremities in Response to Immersing Forearms in Warm Water, *J. Clin. Investigation* 11: 1019, 1932.
5. Grant, R. T., and Pearson, R. S. B.: The Blood Circulation in the Human Limb; Observations on the Differences Between the Proximal and Distal Parts and Remarks on the Regulation of Body Temperature, *Clin. Sc.* 3: 119, 1938.
6. Lewis, T., and Pickering, G. W.: Vasodilatation in Limbs in Response to Warming Body, With Evidence for Sympathetic Vasodilator Nerves in Man, *Heart* 16: 33, 1931.
7. Freeman, N. E.: The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, *Am. J. Physiol.* 113: 384, 1935.
8. Collens, W. S., and Wilensky, N. D.: Use of Intermittent Venous Compression in Treatment of Peripheral Vascular Disease; Preliminary Report, *AM. HEART J.* 11: 705, 1936.
9. Capps, R. B.: Method for Measuring Tone and Reflex Constriction of Capillaries, Venules and Veins of Human Hand With Results in Normal and Diseased States, *J. Clin. Investigation* 15: 229, 1936.
10. Lewis, T., and Grant, R. T.: Observations Upon Reactive Hyperaemia in Man, *Heart* 12: 73, 1925-26.
11. Wilkins, R. W., Weiss, S., and Haynes, F. W.: The Effect of Epinephrin in Circulatory Collapse Induced by Sodium Nitrite, *J. Clin. Investigation* 17: 41, 1938.

THE USE OF MAGNESIUM SULFATE IN THE MEASUREMENT OF CIRCULATION TIME*†

MITCHELL BERNSTEIN, M.D., AND SAMUEL SIMKINS, M.D.
PHILADELPHIA, PA.

THE subject of blood flow has fascinated the medical profession since Harvey's time. It is only within the last decade, however, that methods easily applied clinically have superseded the older, more cumbersome and inaccurate methods for determining the blood velocity, or its inverse equivalent, the circulation time. By the latter term is meant the interval of time necessary for a particle of blood to transverse a given distance.

The methods most commonly used hitherto depend upon the rapid injection of a foreign substance in an antecubital vein and its detection at the point of reaction. The type, as well as the site, of reaction varies considerably with the substance used, viz., the substance's color,¹ vasodilator effect,^{3, 50} radio activity,^{4, 5, 6, 52} effect on respiration,^{4, 7, 8, 9, 10} neuromuscular stimulation,¹¹⁻¹⁴ smell,^{15-19, 49} or taste.^{20, 15, 21-24, 17, 25-32} It is this very difference in results and site of end point that has led to considerable confusion in the literature.

During the course of clinical research with magnesium in cardiovascular-renal disease we were struck with the sharp reaction patients developed during the intravenous injection of a 10 per cent solution of magnesium sulfate. Its possible use as an agent for the determination of the circulation time having suggested itself, we pushed its application in a variety of clinical conditions and finally perfected a standard technique. After the work was well under way, a further perusal of the recently indexed literature disclosed that the use of magnesium as a circulation-time agent had been suggested abroad by Zwillinger³³ and applied, with somewhat different technique from ours, by Nenrath³⁴ in a group of cardiac cases.

PROCEDURE

Five hundred seventy-nine magnesium sulfate circulation-time determinations were performed in 274 patients, 126 of whom were of the cardiac class. Space does not permit the publication of all the data in this study, but illustrative cases are detailed. Most of the subjects were ward patients; a small group of ambulatory hypertensive patients was studied in the outpatient department. Three hundred twenty-nine tests were performed in the cardiac group and 250 in a heterogeneous noncardiac group. To check the efficacy of magnesium, 85 determinations of the cal-

*From the Medical Service of the Senior Author, Jewish Hospital, Philadelphia, Pa. Received for publication Aug. 6, 1938.

†Read before the Jefferson Society for Clinical Investigation, Jefferson Medical College, Philadelphia, Nov. 17, 1938.

cium gluconate circulation time were performed in the cardiac group and 38 in the noncardiac group. Fifty-seven ether circulation-time tests were done in the cardiac cases, and 80 in the noncardiac.

TECHNIQUE

The patient reclines as nearly as possible flat in bed, with the arm at the level of the right auricle. The patient must relax and not hold his breath as this retards the venous return to the heart. He is told that he will experience a transient hot sensation in the pharynx and tongue that spreads rapidly downward, and he is instructed to announce the onset of the sensation in the pharynx at once by crying "now." The tourniquet is applied, the needle inserted, and the injection (slightly warm) given after the lapse of a few seconds. Six cubic centimeters* of a 10 per cent solution of magnesium sulfate are injected as *rapidly as possible* with a needle (preferably 18 gauge) and a 10 c.c. syringe. The time is recorded with a stop watch from the beginning of the injection, rather than at the conclusion or midway during the injection, because even a minimal amount of the drug may evoke a strong reaction in many patients. To insure accuracy when the test is performed by one person unassisted it has been our practice to start the stop watch and to begin the injection at the moment the hand of the stop watch is crossing the five-second mark. The five seconds are subtracted from the circulation time that is finally recorded. In this way the one who performs the test has at his disposal both hands, thus facilitating a rapid, accurate injection. The time required for the completion of the injection is usually less than two seconds. In sensitive patients even as little as 2 c.c. often gives as rapid a circulation time as 6 c.c. On the other hand, repeated trial has shown that 6 c.c. is the optimum amount for consistent results in markedly decompensated patients, the larger quantity being necessary to build up the blood concentration for a sharp end point.

The feeling of heat in the pharynx is extremely sudden in onset and often so intense that in numerous cases the patient's sudden start is indication enough that the end point has been reached. The "heat" follows progressively the course of the peripheral arterial beds, being felt next in the face, one or both hands or perineum, and finally in the feet. This very progressiveness of sensation suggests the possible use of magnesium in measuring the circulation times to the extremities. The sensation is transient, passing off within ten to twenty seconds. The test may be repeated within a few minutes with practically duplicate results. Although we have never observed any magnesium idiosyncrasy to date, we are always provided with an ampoule of a 10 per cent solution of calcium gluconate (the physiologic antagonist of magnesium) for immediate intravenous use should such a reaction occur.

The calcium circulation time is performed in similar fashion, 2.5 c.c. of a 20 per cent solution of calcium gluconate being used as recommended.^{13, 21, 35} To obviate any possibility of the calcium affecting a succeeding magnesium test, and vice versa, we alternated the two agents at random, one test being carried out within a short time after the completion of the preceding one. We observed no effect of one agent upon the other. The sensation produced by calcium is quite similar to that produced by magnesium, though rarely as marked in intensity or suddenness of onset.

The ether circulation time is determined by the intravenous injection of 5 minims of ether mixed with 5 minims of normal saline.¹⁵⁻¹⁸ A tuberculin syringe and a large needle are employed. The time is recorded from the moment of injection until the patient signals that he smells ether on his breath. Usually this is accompanied by a cough or grimace. At the same moment the observer can smell the ether. The ether test thus has the advantage of being both objective and subjective.

*In the early stage of the work ampoules of a 10 per cent solution of magnesium sulfate were purchased on the market. In the latter stages we prepared a 10 per cent C. P. magnesium sulfate solution in distilled water, stored it in ampoule vials, and autoclaved it. This method provided, at practically negligible cost, a solution that gave perfectly satisfactory results.

TABLE I
DETAILED ANALYSIS OF MAGNESIUM AND CALCIUM
CIRCULATION TIMES IN NONCARDIAC GROUP

DIAGNOSIS	NO. OF CASES	NO. OF TESTS MAG.	NO. OF TESTS CALC.	MAGNESIUM CIRCULATION TIME			CALCIUM CIRCULATION TIME		
				LOW (SEC.)	HIGH (SEC.)	AVERAGE (SEC.)	LOW (SEC.)	HIGH (SEC.)	AVERAGE (SEC.)
Normal:	6	11	2	8.6	17.8	13.4			
Cholelithiasis (uncomplicated)	4	7	0	11.2	16.0	13.4			
Diabetes mellitus (uncomplicated)	4	7	2	11.0	12.4	11.8			
Nephropotosis	5	6	2 (1 fail.)	10.8	17.0	13.7	13.0	14.8	13.9
Hepatomegaly (noncardiac)	72	132	16 (2 fail., 1 partial fail.)	7.0	19.8	12.8	10.0	17.2	14.8
Miscellaneous									
Total	91	163	22 (3 fail., 1 partial fail.)	7.0	17.8 (1 ease = 19.8)	12.9	10.0	17.2	14.2
Allergic:									
Bronchial asthma	7	10	3 (1 fail.)	8.2	14.0	11.6			
Hay fever	3	4	1	9.4	16.8	13.5	11.6	17.0	14.5
Vasomotor rhinitis	2	2	0	11.2	13.2	12.2			14.8
Total	12	16	4 (1 fail.)	8.2	16.8	12.1	11.6	17.0	14.6
Active pulmonary tuberculosis	3	3	1 (1 fail.)	11.2	14.8	12.8			16.2
Chronic nephritis (uncomplicated)	3	7	0	7.0	14.0	9.9			
Pernicious anemia (stage of remission)	3	8	3	8.0	17.8	12.7	9.0	15.0	12.6
Secondary anemia	1	2	0	8.6	9.6	9.1			
Pneumonia	14	17	4	8.6	15.2	11.1	9.0	21.4	15.4
Pregnancy	21	33	0	8.4	12.6	11.2			

THE SIGNIFICANCE OF THE CIRCULATION TIME

The magnesium and calcium circulation time (arm-to-tongue time) represents the time required for the blood to travel the pathway from the antecubital vein to the tongue. The ether circulation time (arm-to-lung time) represents the time required for the ether to travel from the antecubital vein to the arterial capillaries of the lung. The lung-to-tongue time is the magnesium or calcium time minus the ether time. The arm-to-tongue time is a measure to the circulation as a whole. The arm-to-lung time is a rough measure of the functional capacity of the right ventricle (that is, its ability to maintain a normal blood velocity through its afferent and efferent vessels). The lung-to-tongue time represents in similar fashion the functional capacity of the left ventricle.

NORMAL INDIVIDUALS

Ninety-one men and women ranging in age from 19 to 70 years were tested (Table I). Excluded from the group were patients with cardiovascular disease, pulmonary or bronchial disease, as well as those with anemia or nephritis, and pregnant women, in whom circulation-time studies with agents other than magnesium have demonstrated departures from "normal."

The average circulation time was 12.9 seconds. The extremes were 7.0 to 17.8 seconds. One patient, perfectly normal in every way (with no evidence of myxedema or polycythemia), showed a reading of 19.8 seconds. Duplicate readings, taken on different days, rarely showed a variation exceeding two seconds. The circulation time is practically unrelated to weight, height, blood pressure, and pulse rate (within normal limits).

HEART DISEASE

The cardiac class numbered 126 and was divided almost equally between men and women. The ages ranged from 16 to 84 years. Two patients were in the ninth decade of life and 15 in the eighth decade. Included were 59 cases of hypertensive heart disease, 46 of arteriosclerotic heart disease, 6 of rheumatic heart disease, and 3 of syphilitic heart disease. A miscellaneous class comprised 2 cases of rheumatic fever (one with coarctation of the aorta), 1 of uncomplicated congenital heart disease, 4 of subacute bacterial endocarditis (3 with old rheumatic heart disease and 1 with congenital heart disease), 3 of thyrotoxic heart disease, and 2 of potential heart disease (electrocardiographic changes only).

There is no agreement in the literature concerning the relationship of the circulation time to the degree of heart failure. Some writers state that a direct proportionality exists between the circulation time and the degree of decompensation; others deny that such a relationship exists. Since no exact studies of this phase of the subject have hitherto been made, we grouped the cardiac patients in six classes

(Table II), under a classification easily adapted to clinical use, as follows: Compensated class, patients totally asymptomatic insofar as decompensation was concerned; Class A, only complaint exertional dyspnea; Class B, exertional dyspnea together with cyanosis; Class C, symptoms of Class A or B, or both, together with pulmonary congestion (as demonstrated by physical or roentgenologic examination); Class D, symptoms and signs of Classes A through C plus enlargement of the liver; Class E, symptoms and signs of Classes A through D plus dependent edema or ascites.

Although this classification may be open to criticism in certain exceptional cases, it is surprising how readily and how accurately cardiac patients may be fitted into one of the above classes by means of circulation-time studies.

Examination of Table III and Fig. 1 shows that as the degree of decompensation increases the circulation time increases steadily from the average of 13.0 seconds found in compensated cardiac patients, until, in Class E, it averages 30.3 seconds. The increase is sharpest in the transition from Class C to Class D and from Class D to Class E. The advent of exertional dyspnea in a cardiac patient is an important sign of approaching decompensation.

Ambulatory compensated patients with hypertension (Table II—Case 21) (Table III) showed a marked decrease of circulation time. That this decrease is not due to an increase in the basal metabolic rate, so often found in hypertension, is shown by the lack of correlation between decreases in the circulation time and such basal metabolic rates as were determined.

The presence of diabetes mellitus (Table II—Case 72) (Table III) seems to play no important role in the circulation time in hypertensive or arteriosclerotic heart disease.

Three patients had syphilitic heart disease, two with huge aneurysms (Table II—Case 97) (Table III). It is well to note the rapid circulation time of 17.8 seconds in a markedly decompensated patient (Table II—Case 226).

MYOCARDIAL INFARCTION, AURICULAR FIBRILLATION, ANGINA PECTORIS AND HEART BLOCK

The circulation time roughly parallels the degree of cardiac decompensation in rheumatic fever (Table II—Case 82) (Table III) and in subacute bacterial endocarditis (Table II—Case 60) (Table III). In congenital heart disease (Table II—Case 154) (Table III) the circulation time is often rapid.² The striking acceleration of the circulation time in hyperthyroidism (Table II—Case 90) (Table III) has been commented upon many times^{13, 20, 36} and is worthy of mention as an important aid in the diagnosis of hyperthyroidism, especially in

obscure cases. It is noteworthy, also, that in patients with hyperthyroidism and cardiac failure the circulation time may fall well within normal limits (Table II—Case 62); in these cases it is the algebraic sum of the hyperthyroid circulation time and that usually expected in a corresponding degree of circulatory failure in patients with no hyperthyroidism.

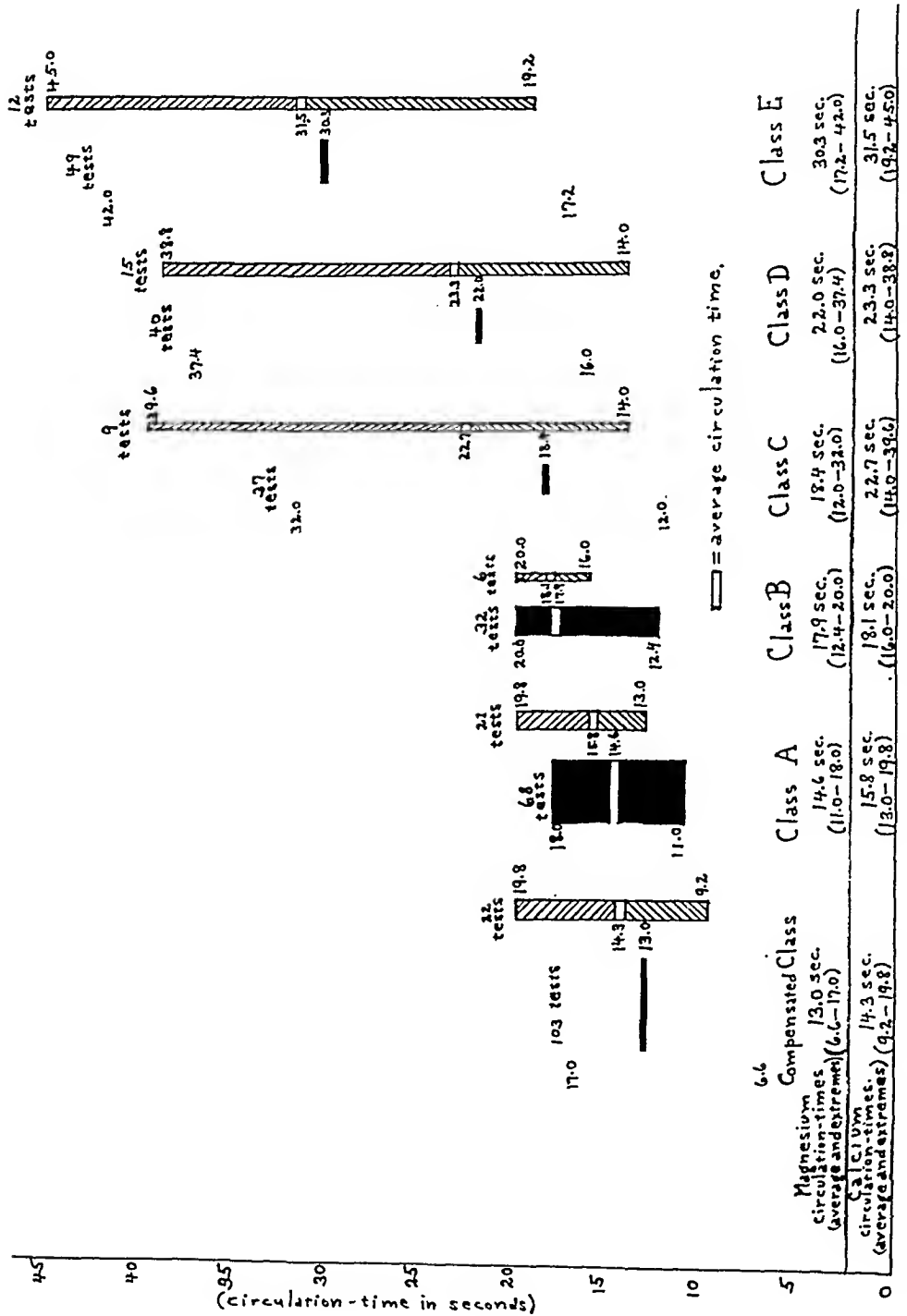


Fig. 1.—Magnesium sulfate and calcium gluconate circulation times in cardiac disease. (See footnote of Table II for explanation.)

TABLE

ILLUSTRATIVE MAGNESIUM SULFATE, CALCIUM GLUCONATE,

CASE NO.	NAME	AGE	SEX	BLOOD PRESSURE	STATUS ON ADMISSION	MAGNESIUM CIRCULATION TIME (ARM-TO-TONGUE TIME) (SEC.)	CALCIUM CIRCULATION TIME (ARM-TO-TONGUE TIME) (SEC.)	ETHER CIRCULATION TIME (ARM-TO LUNG TIME) (SEC.)	MAGNESIUM MINUS ETHER TIME (LUNG-TO-TONGUE TIME) (SEC.)
21	J. G.	40	M	180/100		11/9/37 9.8 (comp.) 11/15/37 10.4 (comp.) 12/17/37 8.4 (comp.) 12/31/37 10.4 (comp.)	11/9/37 16.0—faint end point 12/17/37 10.0—faint end point	11/9/37 8.4	11/9/37 1.4
72	F. G.	58	F	160/ 90	A	13.2 (A) (7) 13.4 (A) (13)	17.2 (7)	8.8 (7)	4.4 (7)
97	R. J.	60	F	164/ 74	A	13.8 (A) (5)	19.0 (5)	—	—
226	H. F.	55	M	154/ 34	E	17.8 (E) (62)	27.0 (62)	9.6 (62)	8.2 (62)
82	E. G.	22	F	200/110	Comp.	14.6 (comp.) (6) 15.6 (comp.) (6)	—	— 9.0 (6)	5.6 (6) 6.6 (6)
60	S. F.	19	M	100/ 60	B	20.0 (D) (15) 26.6 (D) (35) 19.0 (D) (23) 16.0 (D) (38)	23.0 (15)	No end point on several occasions	
154	R. P.	42	F	140/ 78	Comp.	9.8 (comp.) (6) 10.0 (comp.) (14) 9.4 (comp.) (8)	—	—	
90	S. H.	60	F	192/114	Comp.	6.6 (2)	—	—	
62	G. F.	46	F	144/ 84	C	20.0 (C) (6) 16.2 (B) (10)	26.0 (6) 16.0 (9) 16.0 (10)	10.0 (6)	10.0 (6)
231	M. M.	75	F	204/110	D	17.0 (D) (46)	14.0 (46)	5.0 (46)	12.0 (46)
223	L. W.	57	M	140/ 80	Comp.	24.8 (B) (6)	—	—	
131	A. M.	52	M	124/ 90	B	19.0 (B) (1)	—	—	

II
 AND ETHER CIRCULATION TIMES IN CARDIAC DISEASE

CALCIUM MINUS ETHER TIME (LUNG-TO- TONGUE TIME) (SEC.)	ELECTROCARDIOGRAM	X-RAY	REMARKS
11/9/37 7.6	Normal		12/15/37 B.M.R. plus 27%. 2/ 9/38 B.M.R. plus 9%. Hypertensive heart disease. Ambulatory patient.
S.4 (7)	Arteriosclerotic heart disease		Hypertensive heart disease with dia- betes mellitus.
—	Severe myocardial disease Marked left axis devi- ation	Heart enlargement	Ven. pres. (5) = 12.1 cm. saline solu- tion; Wassermann, 4+. Necropsy: colloid goiter; aortic sac, an- eurysm; toxic hyperplasia.
17.4 (62)	Arteriosclerotic heart disease	Heart greatly en- larged Aorta widened	Syphilitic heart disease; aortic regur- gitation, aur. fibrillation; decomp., repeated paracent., thoracic and ab- dominal; Wassermann, 4+.
—	Myocardial changes consistent with con- genital heart dis- ease	Heart N/1 normal in size. Coarcta- tion beginning of transverse aortic arch	Coarctation of aorta. Acute rheumatic fever.
	Right deviation; con- genital heart dis- ease		Congenital heart disease. Post-mortem examination showed pul- monic artery stenosis, patent foramen ovale, and subacute bacterial pul- monary arteritis.
	Normal		Patent ductus arteriosus. Pulmonary infarction.
	Slight myocardial changes		Masked hyperthyroidism; B.M.R. plus 31%. Ven. pres. = 7.8-11; 4 cm. saline; pulse 92.
16.0 (6)	Auricular fibrillation; severe myocardial disease; arboriza- tion block	Heart and lungs normal	Thyroid adenoma, cystic degeneration. Thyrotoxic myocardial degeneration. Aur. fibrillation. Died suddenly 9 days after operation.
9.0 (46)	Auricular fibrillation	Marked cardiac enlargement	Auricular fibrillation. Hypertensive heart disease.
	Auricular fibrillation Marked myocardial fibrosis		Thromboangiitis obliterans; aur. fibril- lation. Arteriosclerotic heart disease.
	Myocardial disease		Severe angina pectoris. Died suddenly in anginal attack (2).

TABLE

CASE NO.	NAME	AGE	SEX	BLOOD PRESSURE	STATUS ON ADMISSION	MAGNESIUM CIRCULATION TIME (ARM-TO-TONGUE TIME) (SEC.)	CALCIUM CIRCULATION TIME (ARM-TO-TONGUE TIME) (SEC.)	ETHER CIRCULATION TIME (ARM-TO-LUNG TIME) (SEC.)	MAGNESIUM MINUS ETHER TIME (LUNG-TO-TONGUE TIME) (SEC.)
221	R. N.	17	M	94/ 60	E	30.0 (E) (35) 34.0 (E) (73) 33.0 (E) (127) 28.8 (E) (217)	40.0 (217) 42.0 (231)	22.0 (217)	6.8 (217)
65	M. G.	54	F	160/110	A	14.3 (A) (3) 12.2 (A) (16) 11.8 (A) (16) 13.4 (A) (4) 12.6 (A) (14)	14.8 (14)	6.0 (10)	6.2 (10)
162	G. R.	28	M	114/ 74	D	37.0 (D) (4) 27.6 (D) (5) 32.8 (D) (7) 28.2 (D) (12) 28.2 (D) (14) 42.0 (E) (18)	38.8 (4)	7.0 (4)	30.4 (4)

Compensated Class (Comp.)—No symptoms or signs of cardiac decompensation.
 Class A—Exertional dyspnea.
 Class B—Dyspnea and cyanosis.
 Class C—Dyspnea, cyanosis, and pulmonary congestion.
 Class D—Symptoms and signs of Classes A-C plus hepatic congestion.
 Class E—Symptoms and signs of Classes A-D plus dependent edema or ascites.

NOTE:—Capital letters refer to cardiac status, as in above legend. Arabic numerals in parentheses refer to the day, after admission of the patient to the hospital, on which the circulation time was performed.

A group of 24 patients with myocardial infarction (Table II—Case 65), as outlined in Table III, showed no striking variations in circulation times from those obtained for the cardiac group as a whole.^{24, 51} The utter lack of harmony between the circulation-time value in auricular fibrillation and the degree of decompensation was shown convincingly in 11 cases—3 of hypertensive heart disease, 3 of rheumatic heart disease, 4 of arteriosclerotic heart disease, and 1 of thyrotoxic heart disease (Table II—Cases 231, 223). The presence of angina pectoris had no effect per se on the circulation time in 7 cases—4 of hypertensive heart disease and 3 of arteriosclerotic heart disease. Magnesium may be used with apparent impunity in these patients. In fact, in one patient with an extreme form of angina pectoris (Table II—Case 131) death occurred suddenly in a severe anginal attack; yet the day previously a magnesium circulation-time test was performed without any reaction whatsoever. No definite relationship between the degree of heart block and the circulation time was noted in 7 cases of heart block—3 of first degree heart block, 2 of right bundle branch block, 1 of transient, almost complete, heart block following an attack of insulin hypoglycemia, and 1 of postscarlatinal heart block (Table II—Case 221³⁷).

II—CONT'D

CALCIUM MINUS ETHER TIME (LUNG-TO- TONGUE TIME) (SEC.)	ELECTROCARDIOGRAM	X-RAY	REMARKS
18.0 (217)	Complete heart block; heart rate 32; pulse 32	Heart considerably enlarged	Complete heart block. Postscarlatinal myocarditis. Bilateral hydrothorax, marked enlarge- ment of liver. Huge ascites.
9.8 (10)	Recent anterior coro- nary thrombosis		Acute infarction, day before admission. Hypertensive heart disease.
31.8 (4)	Severe myocardial disease Auricular fibrillation	Mitral stenotic lesion Heart enlarged	Aur. fibrillation. Post-mortem exam- ination showed mitral stenosis and aortic regurgitation.

BRONCHIAL AND PULMONARY DISEASES

The difficulty of diagnosing cardiac failure with certainty in the presence of pulmonary emphysema offers a baffling clinical problem. The cardinal symptoms—exertional dyspnea, cyanosis, cough, and often dependent edema—are present in both pulmonary emphysema and cardiac failure.^{38, 16} In the differentiation of the two conditions, even electrocardiograms and orthodiagrams may be misleading. The circulation time may be of considerable value here. If rapid, it indicates that the heart is well compensated and is playing no role in the production of the symptoms; if of average duration or of high normal value, it does not necessarily exclude the possibility that heart failure is either primarily responsible for the symptoms or shares the responsibility with the pulmonary emphysema. In our series there were 5 cases of both pulmonary emphysema and arteriosclerotic heart disease (1 patient had bronchiectasis, as well), in which the circulation time matched the cardiac condition rather than the pulmonary. In two additional cases of heart disease and bronchial asthma, cardiac decompensation was excluded by the rapid circulation times obtained.

The accelerated circulation times obtained in 7 cases of bronchial asthma are in accord with other reports.²⁰ In the differentiation of bronchial asthma and so-called cardiac asthma the remarks in the preceding paragraph apply with equal force. No striking aberrations were obtained in pneumonia (6 lobar and 8 bronchopneumonia) or active pulmonary tuberculosis.⁵³

TABLE
DETAILED ANALYSIS OF
CIRCULATION TIMES

DIAGNOSIS	TOTAL			COMPENSATED CLASS				CLASS A			
				MAGNESIUM		CALCIUM		MAGNESIUM		CALCIUM	
	NO. OF PA- TIENTS	NO. OF TESTS		NO. OF TESTS	AV. AND EX- TREMES (SEC.)	NO. OF TESTS	AV. AND EX- TREMES (SEC.)	NO. OF TESTS	AV. AND EX- TREMES (SEC.)	NO. OF TESTS	AV. AND EX- TREMES (SEC.)
		MAG.	CALC.								
Uncomplicated hyperten- sion cases											
A—Ward	19	39	5	8	14.4 (9.4- 17.0)	1	— (19.8)	9	13.4 (11.0- 16.2)	2	17.9 (16.0- 19.8)
B—Outpatient	18	61 1 fail.	18 1 fail.	32	11.5 (8.2- 15.0)	9	12.1 (9.2- 16.0)	26	14.8 (11.0- 18.6)	8	15.2 (12.0- 19.6)
Hypertension with dia- betes mellitus	10	31	8	15	14.5 (11.4- 17.0)	4	15.3 (13.0- 19.8)	2	13.3 (13.2- 13.4)	1	— (17.2)
Arteriosclerotic heart dis- ease	34	69	7	22	13.7 (11.2- 16.2)	5	16.1 (12.0- 20.0)	10	17.3 (14.0- 18.6)	1	— (19.8)
Myocardial infarction											
A—Hypertension	9	22	7	5	14.2 (13.0- 16.0)	—	—	10	13.5 (12.0- 16.8)	4	14.9 (13.0- 16.0)
B—Hypertension and diabetes mellitus	3	4	0	—	—	—	—	—	—	—	—
C—Arteriosclerotic heart disease	12	30	22	8	12.5 (10.8- 15.0)	3 1 fail.	15.1 (12.4- 17.0)	4	15.6 (14.4- 18.0)	3	16.3 (15.0- 18.0)
Total (myocardial infarc- tion)	24	56	29 1 fail.	13	13.1 (10.8- 16.0)	3 1 fail.	15.1 (12.4- 17.0)	14	14.1 (12.0- 18.0)	7	15.5 (13.0- 18.0)
Rheumatic heart disease	6	46	10	1	— (10.0)	—	—	—	—	—	—
Rheumatic fever (coarcta- tion of aorta)	2	3	0	1	— (12.0)	—	—	2	15.1 (14.6- 15.6)	—	—
Syphilitic heart disease	3	3	2 1 fail.	1	— (16.6)	1 fail.	—	1	— (13.8)	1	— (19.0)
Congenital heart disease and subacute bacterial endocarditis	5	12	2	4	11.1 (9.4- 15.0)	—	—	4	11.7 (9.0- 13.0)	1	— (16.0)
Thyrototoxic heart disease	3	5	3	3	9.9 (6.6- 12.2)	—	—	—	—	—	—
Potential heart disease (EKG. changes)	2	3	—	3	12.0 (12.0)	—	—	—	—	—	—
Summary	126	329 1 fail.	85 3 fail.	103 1 fail.	13.0 (6.6- 17.0)	22 3 fail.	14.3 (9.2- 19.8)	68	14.6 (11.0- 18.0)	21	15.8 (13.0- 19.8)

*See footnote of Table II for explanation.

III

MAGNESIUM AND CALCIUM
IN CARDIAC GROUP*

CLASS B				CLASS C				CLASS D				CLASS E			
MAGNESIUM		CALCIUM		MAGNESIUM		CALCIUM		MAGNESIUM		CALCIUM		MAGNESIUM		CALCIUM	
NO. OF TESTS	AV. AND EX-TREMES (SEC.)	NO. OF TESTS	AV. AND EX-TREMES (SEC.)	NO. OF TESTS	AV. AND EX-TREMES (SEC.)	NO. OF TESTS	AV. AND EX-TREMES (SEC.)	NO. OF TESTS	AV. AND EX-TREMES (SEC.)	NO. OF TESTS	AV. AND EX-TREMES (SEC.)	NO. OF TESTS	AV. AND EX-TREMES (SEC.)	NO. OF TESTS	AV. AND EX-TREMES (SEC.)
4	17.5 (12.4-19.4)	1	— (17.6)	8	17.5 (12.0-25.0)	—	—	8	21.7 (17.0-23.8)	1	— (14.0)	2	30.3 (21.0-39.6)	—	—
1	— (18.6)	—	—	1	— (21.0)	1	— (39.6)	—	—	—	—	—	—	—	—
6	16.1 (14.2-20.0)	—	—	—	—	—	—	2	17.0 (16.0-18.0)	2	22.7 (22.6-22.8)	6	24.3 (21.4-27.2)	1	— (29.6)
11	20.1 (16.0-24.8)	—	—	14	21.0 (16.0-32.0)	—	—	11	20.8 (17.0-28.0)	—	—	1	— (17.8)	1	— (27.0)
2	16.7 (16.2-17.2)	1	— (20.0)	5	17.7 (15.2-23.0)	1	— (24.0)	—	—	1	— (27.8)	—	—	—	—
1	— (14.0)	—	—	2	12.3 (12.0-12.6)	—	—	1	— (19.0)	—	—	—	—	—	—
6	21.5 (17.0-26.2)	1	— (19.0)	6	20.8 (15.0-32.0)	6	14.1 (14.0-19.8)	8	20.3 (16.0-24.6)	9	22.3 (16.0-35.0)	—	—	—	—
9	20.3 (16.2-26.2)	2	19.5 (19.0-20.0)	13	18.3 (12.0-32.0)	7	19.8 (14.0-24.0)	9	20.1 (16.0-24.6)	10	22.9 (16.0-35.0)	—	—	—	—
—	—	—	—	—	—	—	—	6	29.9 (25.2-37.4)	1	— (38.8)	39	31.7 (17.2-42.0)	9	32.8 (19.2-45.0)
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	1	— (17.8)	1	— (27.0)
—	—	—	—	—	—	—	—	4	20.4 (16.0-26.6)	1	— (23.0)	—	—	—	—
1	— (16.2)	2	16.0 (16.0)	1	— (20.0)	1	— (26.0)	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
32	17.9 (12.4-20.0)	6	18.1 (16.0-20.0)	37	18.4 (12.0-32.0)	9	22.7 (14.0-39.6)	40	22.0 (16.0-37.4)	15	23.3 (14.0-38.8)	49	30.3 (17.2-42.0)	12	31.5 (19.2-45.0)

MISCELLANEOUS CLINICAL CONDITIONS

Normal readings were obtained in small groups of cases of cholelithiasis, nephroptosis, uncomplicated diabetes mellitus, and pernicious anemia in the stage of remission. One patient with marked secondary anemia showed rapid circulation times.³⁹ Six patients with chronic glomerulonephritis, 3 uncomplicated and 3 with myocardial disease, showed nothing striking in circulation-time studies. No toxic effects were observed.⁴⁰

In 5 patients with enlargement of the liver due to portal cirrhosis, arsphenamine hepatitis, or secondary carcinoma, the circulation times were normal. Jaundice is no deterrent to the use of the test; when it is present the circulation time may be of great value in differentiating enlargement of the liver due to cardiac from that due to extra-cardiac disease.

PREGNANCY

In 21 cases of pregnancy, nearly all of which were studied just prior to active labor, there was a marked increase in blood velocity, which is a clear indication of the burden pregnancy places upon the circulation. It is surprising to find that work done with other circulation-time agents indicated a slight but progressive retardation of blood flow in pregnancy.²²

COMPARISON OF MAGNESIUM AND CALCIUM AS CIRCULATION-TIME AGENTS

A glance at Table II shows numerous discrepancies between the magnesium and calcium arm-to-tongue circulation times in the same individual. Table III and Fig. 1 sum up the differences. Almost invariably the calcium time was longer. The reaction with magnesium is extremely sharp, so sharp in many cases as to afford an objective, as well as subjective, reaction. In the normal group the differences are not so marked except in a few cases (the calcium time ranging from eight-tenths to eight seconds longer than the corresponding magnesium time). In the cardiac groups the differences were more pronounced, being accentuated, in a general way, as the degree of decompensation increased. The discrepancies often ran as high as twelve to fifteen seconds. Therefore, especially in classes A and B, in which the diagnosis of cardiac decompensation is so often difficult to make clinically, the abnormally long calcium lung-to-tongue times may lead to erroneous diagnoses of left-sided heart failure.

The empirical fear of most clinicians of intravenous calcium therapy has recently been amply substantiated, both in reports on human beings^{41, 54} and in animal experiments.⁴²⁻⁴⁶ Electrocardiographic studies of the normal human heart show in a large percentage of subjects marked changes in the T- and P-waves, as well as occasional cardiac

arrest.³⁵ Similar studies, following calcium intravenously, in cases of heart disease are not available. There can be very little question of the toxic effects from the combined use of calcium and digitalis. Changes in the heart rate after therapeutic doses of calcium, ventricular fibrillation after toxic doses, and even sudden fatalities in patients who received calcium intravenously after previous administrations of digitalis have been reported.⁴⁷

"Study indicates the hazard existing in the use of calcium gluconate intravenously following digitalis. . . . The conclusion is reached that great caution is to be used in giving calcium intravenously with or shortly after digitalis. It is apparently not safe to use this combination in patients who have received small doses of digitalis."⁴²

All observers are in accord that *calcium must be injected slowly* to minimize its toxic effects.^{35, 48} And yet, when used as a circulation-time agent, calcium must be injected as rapidly as possible. In the present series, an intravenous injection of calcium hastened the death within a few hours of a patient who had been digitalized and was in fairly good condition prior to the injection. A few years ago the junior author had a similar experience with a digitalized hypertensive patient who was given an intravenous calcium injection after a cholecystectomy and died suddenly during the course of the injection (case unreported).

On the other hand, the intravenous injection of magnesium has no deleterious action on the heart. A study of 100 patients, of whom many were seriously ill cardiac patients, with electrocardiographic tracings taken concurrently with the magnesium injections, revealed no evidence of myocardial damage.* In many of these patients, 10 to 20 c.c. of a 10 per cent solution of magnesium sulfate were injected rapidly with no ill effects. Practically all patients with decompensation received digitalis both orally and parenterally, many up to the point of complete digitalization, with no toxic effects.

A surprising feature in our experience was the occurrence of 7 failures and 1 partial failure (the patient feeling the heat sensation in the back only, 40 seconds after the beginning of the injection) in 123 calcium injections. It is curious that no mention of such failures has been made by other authors. In the magnesium group (579 tests) there was 1 failure (a young patient with hypertension who reacted normally in subsequent tests).

CRITERIA

Magnesium sulfate fulfills well the criteria proposed for the ideal circulation-time agent. It is nontoxic in the dose employed. It does not influence blood velocity until the end reaction has occurred—this despite the fact that in many patients with hypertension and in some

*Detailed report to be published subsequently.

without hypertension a sharp fall of both diastolic and systolic pressure occurs immediately after an injection. That this change in blood pressure is compensated for by the circulatory mechanism is attested by the fact that circulation times, repeated within two or three minutes, show almost duplicate values. Accidental paravenous infiltration produces no pain, venous thrombosis, or slough. The magnesium is eliminated rapidly through the kidneys. The end reaction is readily discernible in normal and pathologic conditions and is so sharp that the test in many patients becomes practically objective as well as subjective. And lastly, the cost of the reagent (chemically pure magnesium sulfate) is practically negligible; it is possible to prepare large autoclaved quantities in ampoule vials so cheaply that the general practitioner has at his command, for bedside or office use, a valuable, easily applied addition to his diagnostic armamentarium.

TABLE IV
ETHER CIRCULATION TIME*
(Fifty-Six Noncardiac Patients; Forty Cardiac Patients)

NO. OF TESTS	ETHER TIME (ARM-TO-LUNG TIME) (SEC.)	MAG- NESIUM MINUS ETHER (LUNG-TO-TONGUE TIME) (SEC.)	CALCIUM MINUS ETHER (LUNG-TO-TONGUE TIME) (SEC.)	NO. OF TESTS	ETHER TIME (ARM-TO-LUNG TIME) (SEC.)	MAG- NESIUM MINUS ETHER (LUNG-TO-TONGUE TIME) (SEC.)	CALCIUM MINUS ETHER (LUNG-TO-TONGUE TIME) (SEC.)
<i>Noncardiac Class</i>				<i>Compensated Cardiac Class</i>			
80	5.7 (2.6-9.0) 1 test = 10.0	5.1 (2.2-10.8)	7.6 (3.4-12.2)	14	7.3 (5.0-10.0)	5.8 (2.4-9.2)	8.3 (6.0-11.4)
<i>Class A</i>				<i>Classes B to E</i>			
14	6.7 (5.2-9.6)	6.3 (2.4-11.0)	8.8 (3.4-11.8)	28 (1 fail.)	— (5.0-22.0)	— (2.6-30.4)	— (11.8-31.8)

*See footnote of Table II for explanation.

THE ETHER CIRCULATION TIME AND LUNG-TO-TONGUE TIME

The ether times in the noncardiac group and in the compensated and Class A groups of the cardiac series were approximately equal (Table IV). In the other cardiac groups the ether time was either normal or greatly prolonged, depending on whether the functional integrity of the right heart was intact or impaired. In one case (Table II—Case 60) of congenital heart disease with a superimposed subacute bacterial pulmonary arteritis, repeated trials failed to produce an ether end point. The magnesium lung-to-tongue time was appreciably shorter than the calcium lung-to-tongue time on account of the correspondingly smaller values for the magnesium arm-to-tongue time.

DISCUSSION

The circulation time is of greatest clinical interest in cardiac decompensation, the condition par excellence in which a slowing of the blood velocity occurs. As has been shown, it is the status of the circulation, irrespective of the etiological factors or mechanical status of the heart, that determines the blood velocity. The presence of heart disease per se, irrespective of etiology, does not influence the blood velocity. Likewise, the presence of such mechanical factors as auricular fibrillation or mitral stenosis plays no important role. It is only when decompensation occurs that the circulation time changes. A detailed analysis of our results shows clearly that the circulation time is *not* the infallible diagnostic tool it was originally believed to be. A rapid circulation time (excluding the presence of uncomplicated hyperthyroidism, marked anemia, or high fever) excludes cardiac decompensation. However, much more common than has been believed is the occurrence of normal circulation times in markedly decompensated patients. In general, as the degree of decompensation increases, the circulation time increases, but not in strict proportionality, so that the absolute value of the individual test does not necessarily reflect the clinical status in any case. More important than the absolute value of the circulation time in any individual is the change in circulation time from time to time in that individual. This is well illustrated by Table II—Case 162; the patient's rapid change for the worse, at the end, was heralded by a corresponding increase in the circulation time. In this respect, as a teleologic agent, the test is of great value.

The test may also be of importance in separating edema and ascites of cardiac origin from that of extracardiac origin. Of similar import is its use in noncardiac hepatomegalies.

The results obtained demonstrate conclusively that magnesium is preferable to calcium as an agent in the determination of the circulation time. This holds true because of its sharpness of reaction and shorter reaction time, lack of deleterious action on the heart, and dependability.

CONCLUSIONS

1. The use of a 10 per cent solution of magnesium sulfate as an agent for the determination of the circulation time is described. Five hundred seventy-nine magnesium sulfate tests were performed in 274 patients, of whom 126 were cardiac and 146 noncardiac patients. As a check, 123 calcium gluconate circulation-time tests, as well as 137 ether tests, were performed.

2. The technique of the test is presented in detail.

3. In 91 "normal" subjects, representing a wide diversity of noncardiac conditions, the average circulation time was 12.9 seconds. The extremes were 7.0 and 17.8 seconds.

4. In the cardiac group, the ages ranged from 16 to 84 years; 2 patients were in the ninth decade of life and 15 in the eighth decade.

5. The cardiac group included 59 cases of hypertensive heart disease, 46 of arteriosclerotic heart disease, 6 of rheumatic heart disease, and 3 of syphilitic heart disease. A miscellaneous group comprised 2 cases of rheumatic fever (one with coarctation of the aorta), 1 of uncomplicated congenital heart disease, 4 of subacute bacterial endocarditis (3 with old rheumatic heart disease and 1 with congenital heart disease), 3 of thyrotoxic heart disease, and 2 of potential heart disease.

6. The cardiac group was divided into six classes, varying in the degree of compensation, under a classification easily adapted to clinical use. A detailed correlation of the circulation tests with this grouping establishes the fact that, as a whole, the circulation time increases steadily as the degree of decompensation increases, but that there is no strict proportionality between the circulation time and the degree of decompensation.

7. Ambulatory compensated patients with hypertension have a rapid blood velocity.

8. Diabetes mellitus per se has no effect on the circulation time.

9. The blood velocity is determined to a great extent by the status of the circulation, irrespective of the etiological factors involved, such as hypertensive, arteriosclerotic, rheumatic, or syphilitic heart disease, or the presence of mechanical factors, such as auricular fibrillation.

10. The presence of a high normal circulation time is common in advanced degrees of cardiac decompensation. Consequently, the circulation time is of limited value in the diagnosis of cardiac decompensation.

11. The change in blood velocity from time to time in the same patient is of much more importance than the absolute value of the circulation time, and may be of great teleologic importance.

12. Magnesium sulfate is totally innocuous in angina pectoris, heart block, myocardial infarction and nephritis.

13. It may be of help, within certain limits, in differentiating pulmonary emphysema and myocardial failure, as well as bronchial asthma and cardiac asthma. It may be of value also in separating hepatomegaly of cardiac origin from that of extracardiac origin. The test may be used safely in the presence of jaundice.

14. The circulation time is rapid in hyperthyroidism, pneumonia, marked anemia, and pregnancy. It is normal in active pulmonary tuberculosis and normal or somewhat rapid in bronchial asthma.

15. Conclusive evidence is given of the marked superiority of magnesium over calcium as a circulation-time agent.

16. The intravenous injection of magnesium has no deleterious effect on the heart, as shown by electrocardiographic tracings made on 100

patients during the injection. The magnesium circulation test is harmless in digitalized patients.

17. The ether time in normal subjects and in cardiac patients with incipient decompensation is normal, averaging 5.7 seconds, with extremes from 2.6 to 10 seconds. The ether time is increased in right-sided heart failure, and the lung-to-tongue time (magnesium circulation time minus ether time) is increased in left-sided heart failure.

18. The magnesium sulfate circulation test is well adapted for bedside and office use, thus affording a valuable diagnostic aid for the general practitioner.

The authors wish to thank Doctors J. C. Doane, E. A. Heller, C. J. Stamm, and P. Williams for the opportunity of studying a few of their patients.

REFERENCES

1. Koeh, E.: Die Stromgeschwindigkeit des Blutes. Ein Beitrag zur Arbeitsprüfung des Kreislaufes, *Deutsches Arch. f. klin. Med.* 140: 39, 1922.
2. McGuire, J., and Goldman, F.: Apparent Increased Velocity of Blood Flow in Cases of Congenital Heart Disease With Septal Defects Having Right-to-Left Shunt, *AM. HEART J.* 14: 230, 1937.
3. Bartels, E. C., and Powelson, M. H.: The Rate of the Circulation of the Blood in Vascular Diseases as Determined by the Use of Histamine, *Proc. Staff Meet., Mayo Clin.* 4: 217, 1929.
4. Robb, G. P., and Weiss, S.: A Method for the Measurement of the Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man, *AM. HEART J.* 8: 650, 1933.
5. Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow. II. The Velocity of Blood Flow in Normal Resting Individuals and Critique of the Method Used, *J. Clin. Investigation* 4: 15, 1927.
6. Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow. VII. The Pulmonary Circulation Time in Normal Resting Individuals, *J. Clin. Investigation* 4: 399, 1927.
7. Robb, G. P., and Weiss, S.: The Velocity of Pulmonary and Peripheral Venous Blood Flow and Related Aspects of the Circulation in Cardiovascular Disease, *AM. HEART J.* 9: 742, 1934.
8. Kopp, I.: The Arm to Carotid Circulation Time in Prolonged Therapeutic Fever, *AM. HEART J.* 11: 667, 1936.
9. Loevenhart, A. S., Lorenz, W. F., Martiu, H. G., and Malone, J. Y.: Stimulation of the Respiration by Sodium Cyanid and Its Clinical Application, *Arch. Int. Med.* 21: 109, 1918.
10. Loevenhart, A. S., Schlomovitz, B. H., and Seybold, F. G.: The Determination of the Circulation Time in Rabbits and Dogs and Its Relation to the Reaction Time of the Respiration to Sodium Cyanide, *J. Pharmacol. and Exper. Therap.* 19: 221, 1922.
11. Spier, L. C., Wright, I. S., and Saylor, L.: A New Method for Determining the Circulation Time Throughout the Vascular System, *AM. HEART J.* 12: 511, 1936.
12. Goldberg, S. J.: The Use of Calcium Gluconate as a Circulation Time Test, *Am. J. M. Sc.* 192: 36, 1936.
13. Goldberg, S. J.: Circulation Time as a Diagnostic Aid in Hyperthyroidism, *Ann. Int. Med.* 11: 1818, 1938.
14. Kahler, H.: Über Veränderungen der Blutumlaufzeit, *Wien. Arch. f. inn. Med.* 19: 1, 1929-1930.
15. Hitzig, W.: The Use of Ether in Measuring the Circulation Time from the Antecubital Veins to the Pulmonary Capillaries, *AM. HEART J.* 10: 1080, 1935.
16. Oppenheimer, B. S., and Hitzig, W. M.: The Use of Circulatory Measurements in Evaluating Pulmonary and Cardiac Factors in Chronic Lung Disorders, *AM. HEART J.* 12: 257, 1936.

17. Hitzig, W. M., King, F. H., and Fishberg, A. M.: Circulation Time in Failure of the Left Side of the Heart, *Arch. Int. Med.* 55: 112, 1935.
18. Hitzig, W. M.: Measurement of Circulation Time from Antecubital Veins to Pulmonary Capillaries, *Proc. Soc. Exper. Biol. & Med.* 31: 935, 1934.
19. Miller, H. R.: The Velocity of Blood Flow in Part of the Pulmonary Circulation, *Proc. Soc. Exper. Biol. & Med.* 31: 942, 1934.
20. Tarr, L., Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, *AM. HEART J.* 8: 766, 1933.
21. Baer, S., and Slipakoff, B. G.: Measurement of Circulation Times and the Used in Their Determination, *AM. HEART J.* 16: 29, 1938.
22. Greenstein, N. M., and Clahr, J.: Circulation Time Studies in Pregnant Women, *Am. J. Obst. & Gynec.* 33: 414, 1937.
23. Candel, S., and Rabinowitz, M. A.: Blood Velocity Rate and Venous Pressure in the Prognosis of Heart Disease, *Ann. Int. Med.* 10: 1000, 1937.
24. Fishberg, A. M., Hitzig, W. M., and King, F. H.: Circulatory Dynamics in Myocardial Infarction, *Arch. Int. Med.* 54: 997, 1934.
25. Macy, J. W., Claiborne, T. S., and Hurxthal, L. M.: The Circulation Rate in Relation to Metabolism in Thyroid and Pituitary States (Decholin Method), *J. Clin. Investigation* 15: 37, 1936.
26. Kremer, M., and Robertson, J. D.: Estimation of the Arm to Tongue Circulation Time by Means of Decholin and Comparison With the Basal Metabolic Rate, *J. Physiol.* 85: 24P, 1935.
27. Drennan, L. M., Jr.: The Clinical Significance of the Blood Circulation Time as Determined by the Saccharin Test, *M. Ann. District of Columbia* 5: 238, 1936.
28. Winternitz, M., Deutsch, J., and Brüll, Z.: Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholininjektion, *Med. Klin.* 27: 986, 1931.
29. Winternitz, M., Deutsch, J., and Brüll, Z.: Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholininjektion, *Med. Klin.* 28: 831, 1932.
30. Wilcox, A.: The Circulation Rate: Its Estimation and Clinical Application, *Middlesex Hosp. J.* 37: 81, 1937.
31. Gargill, S. L.: The Use of Sodium Dehydrocholate as a Clinical Test of the Velocity of Blood Flow, *New England J. Med.* 209: 1089, 1933.
32. Fishberg, A. M., Hitzig, W. M., and King, F. H.: Measurement of the Circulation Time With Saccharin, *Proc. Soc. Exper. Biol. & Med.* 30: 651, 1933.
33. Zwillinger, L.: Über die Magnesiumwirkung auf das Herz, *Klin. Wchnschr.* 14: 1429, 1935.
34. Neurath, O.: Untersuchungen über die Bestimmung der Blutumlaufgeschwindigkeit mit Magnesiumsulfat, *Ztschr. f. klin. Med.* 132: 134, 1937.
35. Berliner, K.: The Effect of Calcium Injections on the Human Heart, *Am. J. M. Sc.* 191: 117, 1936.
36. Blumgart, H. L., Gargill, S. L., and Gilligan, D. R.: Studies on the Velocity of Blood Flow. XIII. The Circulatory Response to Thyrotoxicosis, *J. Clin. Investigation* 9: 69, 1930.
37. Bernstein, Mitchell: Auriculoventricular Dissociation Following Scarlet Fever, *AM. HEART J.* 16: 582, 1938.
38. Kountz, W. B., Alexander, H. L., and Prinzmetal, M.: The Heart in Emphysema, *AM. HEART J.* 11: 163, 1936.
39. Blumgart, H. L., Gargill, S. L., and Gilligan, D. R.: Studies on the Velocity of Blood Flow. XV. The Velocity of Blood Flow and Other Aspects of the Circulation in Patients With Primary and Secondary Anemias and in Two Patients With Polycythemia Vera, *J. Clin. Investigation* 9: 679, 1931.
40. Hirschfelder, A. D.: Clinical Manifestations of High and Low Plasma Magnesium, *J. A. M. A.* 102: 1138, 1934.
41. Lloyd, W. D. M.: Danger of Intravenous Calcium Therapy, *Brit. M. J.* 1: 662, 1928.
42. Golden, J. S., and Brams, W. A.: Mechanism of the Toxic Effects From Combined Use of Calcium and Digitalis, *Ann. Int. Med.* 11: 1084, 1938.
43. Fröhlich, A., and Gussenbauer, R.: Die Wirkung der Erdalkalien auf das Elektrogramm normaler und oxalatvergifteter Kaninchen, *Arch. f. exper. Path. u. Pharmakol.* 97: 61, 1923.

44. Leontowitsch, A.: Elektrokardiogrammstudien über die Wirkung der calciumsalzeder Ringer'sehen Lösung aufs Herz, Arch. f. d. ges. Physiol. 147: 473, 1912.
45. Kraus, F.: Ueber die Wirkung des Kalziums auf den Kreislauf, Deutsche med. Wchnsehr. 46: 201, 1920.
46. Hoff, H. E., and Nahum, L. H.: An Analysis of the Cardiac Irregularities Produced by Calcium and Their Prevention by Sodium Amytal, J. Pharmacol. & Exper. Therap. 60: 425, 1937.
47. Bower, J. O., and Mengle, H. A. K.: The Additive Effect of Calcium and Digitalis, J. A. M. A. 106: 1151, 1936.
48. Aub, J. C.: The Use of Calcium and the Choice of a Calcium Salt, J. A. M. A. 109: 1277, 1937.
49. Lian, C., and Facquet, J.: La mesure de la vitesse circulatoire avec l'ether, la saccharine et la fluoresceine dans les principaux types d'insuffisance cardiaque, Bull. et mém. Soc. méd. d. hôp. de Paris 52: 428, 1936.
50. Weiss, S., Robb, G. P., and Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease as Measured by the Effect of Histamine on the Minute Vessels, AM. HEART J. 4: 664, 1929.
51. Master, A. M., Dack, S., and Jaffe, H. L.: Coronary Thrombosis: An Investigation of Heart Failure and Other Factors in Its Course and Prognosis, AM. HEART J. 13: 330, 1937.
52. Blumgart, H. L., and Yens, O. C.: Studies on the Velocity of Blood Flow. I. The Method Utilized, J. Clin. Investigation 4: 1, 1927.
53. Hurst, A., and Brand, M. A.: A Study of Venous Pressure and Circulation Time in Pulmonary Tuberculosis, J. Thoracic Surg. 6: 638, 1937.
54. Walters, W., and Bowler, P.: Pre-Operative Preparation of Patients With Obstructive Jaundice. An Experimental Study of the Toxicity of Intravenous Calcium Chloride Used in the Preparation of Patients, Surg. Gynec. and Obst. 39: 200, 1924.

Department of Clinical Reports

GLOMUS TUMOR

REPORT OF A CASE

SAMUEL BLINDER, M.D.

NEW YORK, N. Y.

ALTHOUGH Masson¹ first presented a histopathologic conception of glomus tumors as early as 1924, and although numerous authentic cases have, since then, been reported in the foreign literature,² it was not until 1934 that the first case report appeared in the American literature.³ Lesions clinically identical with glomus tumor have been described under various headings, such as hemangioma, subungual tumors, and exostoses, etc., since 1812.⁴ Up to the time our patient was first seen (August, 1936), there were about seventy cases on record.⁵⁻¹⁵ With advancement in knowledge of the subject, the diagnosis has become much more obvious, and there has naturally been a relative increase in the number of cases reported. We wish to add ours to this group, particularly as we had the opportunity to observe the patient over a period of eighteen months after operation.

Because of the scarcity of reports of this tumor, it seemed desirable to present a brief general description of the histologic structure of the glomus itself before reporting the present case. A glomus is a specialized arteriovenous anastomosis.¹⁶ It may appear almost anywhere over the cutaneous surfaces of the body and in the subungual regions, but is by far most frequently encountered in the extremities. Depending on the location, a glomus may vary in width from 60 to 220 microns. The glomus undergoes considerable alteration with age. It is formed imperfectly at birth, reaches maximum development in young adult life, and atrophies in old age. It is distributed widely among other mammals in much the same regions as in man. A significant fact is that the glomus has not been described in cold-blooded animals, yet it is very prominent in birds whose body temperature is above that of mammals.

The cutaneous glomus occupies a specific zone of the cutis—the stratum reticulare. Briefly, it consists of the following: an afferent artery, carrying blood from the interior of the body; a canal called the Suquet-Hoyer canal, connecting the artery with the vein; pre-glomic arterioles nourishing all the constituents of the glomus; a clear periglomic zone or expansion zone furnished with a neuroreticular

mechanism which controls the function of the Suquet-Hoyer canal; a specially arranged system of collecting veins; and an outer lamellated collagenous zone surrounding the entire glomus. Collecting venules are provided with septa or valves, and each channel communicates with that of the main collecting vein (Fig. 1). The cutaneous glomus is so named because of its similarity to the glomus coccygeum and its homologues.

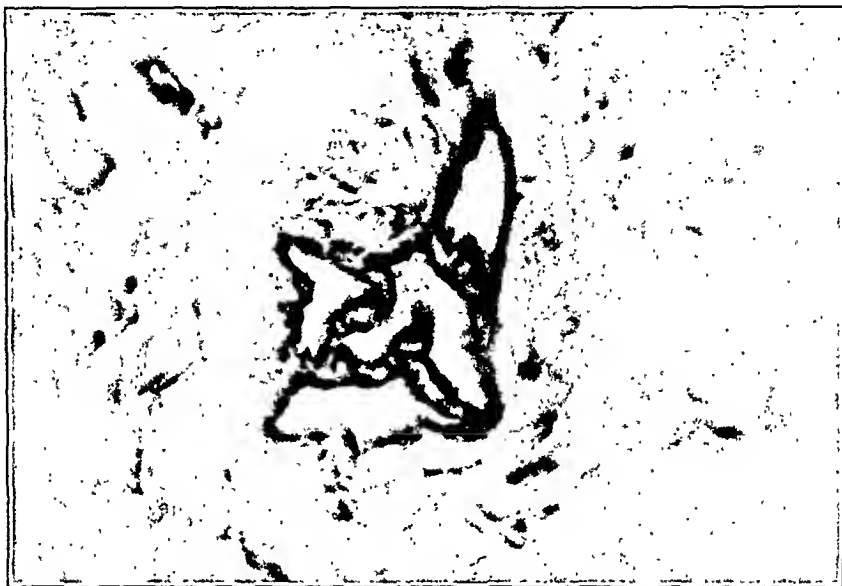


Fig. 1.—Cross section showing the septa or valves in the venules. Hematoxylin and eosin stain ($\times 200$).

CASE REPORT

History.—Mr. R., an executive, aged thirty-eight years, had noticed a purple-bluish spot under the lower inner corner of the nail of the left index finger for fifteen to twenty years previous to his examination on Aug. 14, 1936. During this time he had suffered paroxysms of shooting pain in the tip of the finger, radiating to the forearm and arm and occasionally reaching the shoulder. The pain was markedly aggravated by cold weather and relieved by warm weather or by immersion of the finger in hot water. The slightest pressure exerted over the purple-bluish spot evoked excruciating pain. In recent years the condition had become much more painful. There had been no increase in size of the tumor area with passage of time under normal conditions, nor did it enlarge during the paroxysmal attacks. All sorts of therapy, including superficial curettement, had been employed without improvement. There was no history of trauma. The patient was a total abstainer from tobacco and drank only occasionally. The past history was otherwise entirely negative.

Examination showed a purple-bluish discoloration about one-fourth of an inch in its longitudinal diameter, located under the lower inner corner of the nail of the left index finger. There were no thermal changes and a detailed study of the nail fold capillaries did not reveal any abnormalities. A roentgenogram of the finger failed to show an area of depression in the bone or other evidence of pathologic change. Pressure over the tumor area or immersion of the finger in ice-cold water produced excruciating pain.

Fig. 2.

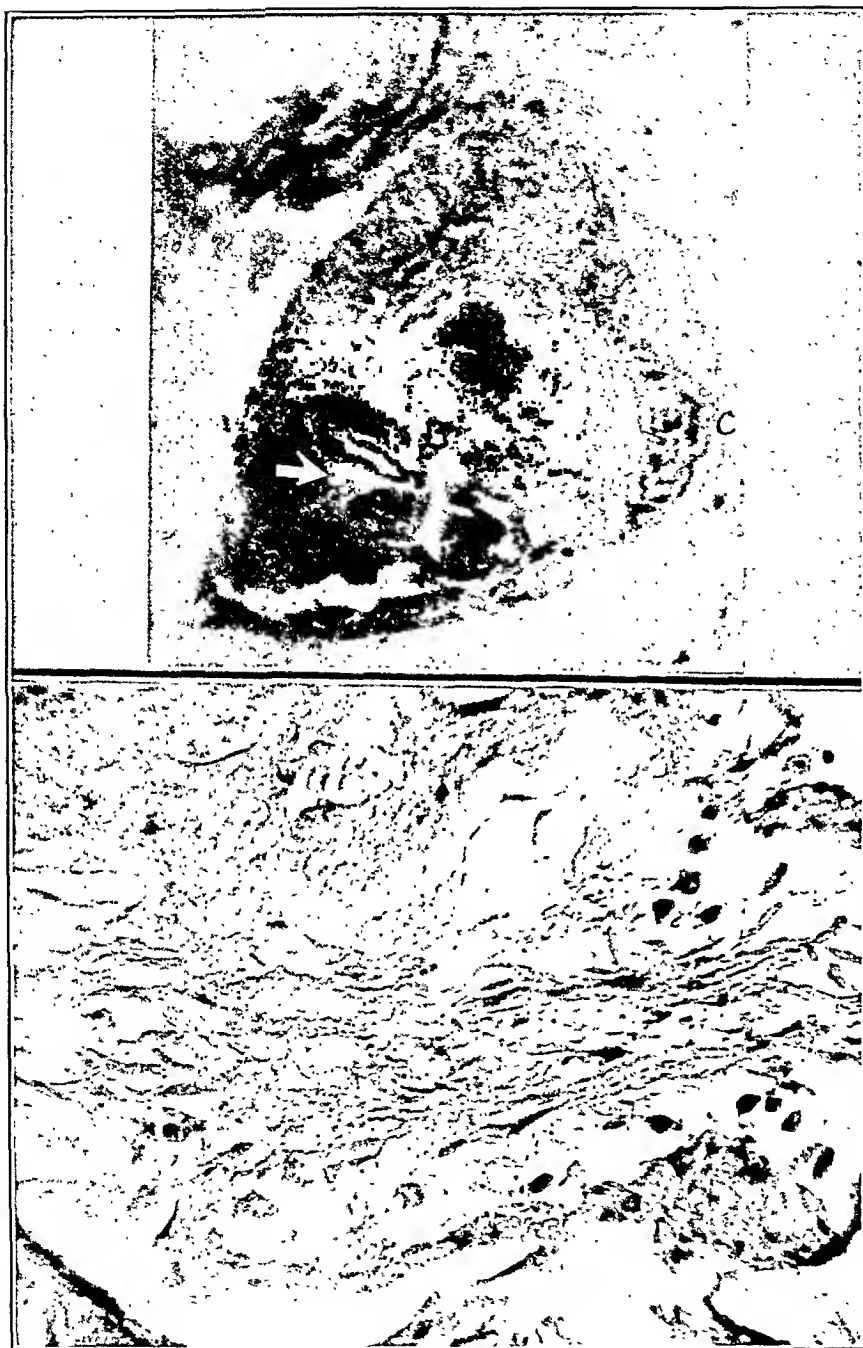


Fig. 3.

Fig. 2.—Cross section through entire tumor mass showing the sinusoidal canals. The artery can be seen in the tumor, while the collecting vein is seen at its edge. A, artery; B, sinusoidal canal; C, collecting vein. Hematoxylin and eosin stains ($\times 160$).

Fig. 3.—Nerve fibers running between masses of tumor cells. A blood vessel lined with swollen endothelial cells is seen at the lower part of the section. Weigert's stain ($\times 1600$).

Course.—The patient was operated on by Dr. Louis R. Davidson at the New York Post Graduate Hospital Oct. 7, 1936. Under block anesthesia with 2 per cent novocain, the ulnar aspect of the nail bed and the matrix were removed with the glomus tumor and two interrupted sutures were employed distally and proximally for hemostasis. Black silk suture material was used for the skin. Local pain was present for several days after operation, and healing was complete in one week.

Pathology.—This study was carried out and reported as follows by Dr. Louise H. Meeker. *Gross examination* indicated the specimen measured 28 by 18 by 8 mm. One surface was covered by a portion of nail, about which there were a few millimeters of skin. The nail bed was included, and beneath the bluish area seen in the nail there was a small bluish circumscribed area a few millimeters in diameter, somewhat different in appearance from the surrounding fibrous tissue. On *microscopic examination* stained sections showed a central area formed of ramifying sinusoidal canals (as in cavernous hemangiomata), separated by bands of epithelioid cells which were supported by strands of collagen fibers (Fig. 2). Between the epithelioid cells were strands of nonmyelinated nerve fibers which were easily demonstrated by special nerve tissue stains, such as Weigert's (Fig. 3). The epithelioid cells were much more numerous than the other tissues. They formed wide mantles over the septa between the vascular channels. The epithelioid character of the cells was emphasized by the formation of cell bridges. Surrounding this central area was a layer of connective tissue, forming a pseudocapsule in which arterioles and small veins were scattered.

COMMENT

Glomus tumors are benign arterial neuromyomatous lesions of the glomus, a structure normally present in man and warm-blooded mammals. The history of the existence of a purple-bluish or reddish area of discoloration, commonly located under the nail bed but sometimes found elsewhere, which has been present for a long time and is associated with characteristic paroxysms of local pain, makes the clinical diagnosis readily apparent.

SUMMARY

The case of a patient with a glomus tumor is presented. Examination eighteen months subsequent to complete surgical removal shows apparently permanent recovery. This result confirms those obtained in all cases previously reported. Once the diagnosis has been established, immediate surgical removal is advised.

I wish to express my appreciation to Dr. A. Wilbur Duryee and Dr. Irving S. Wright who aided in the diagnosis and study of this case.

REFERENCES

1. Masson, P.: *Le Glomus neuromyo-artériel des régions tactiles et ses tumeurs*, Lyon chir. 21: 257, 1924.
2. Stratmann, E. A.: *Über seltene Tumoren im Nagelbett, Neuromyoarterielle Glomustumoren oder arterielle Angioneuromyome*, Dermat. Ztschr. 67: 129, 1933.
3. Mason, M. L., and Weil, A.: *Tumor of Subcutaneous Glomus*, Surg. Gynec. & Obst. 58: 807, 1934.
4. Wood, W.: *On Painful Subcutaneous Tubercle*, Edinburgh M. and S. J. 8: 283, 1812.

5. Keasbey, L. E.: Tumors of Glomus, *Internat. J. Med. & Surg.* 46: 431, 1933.
6. Adair, F. E.: Glomus Tumor; Clinical Study With Report of 10 Cases, *Am. J. Surg.* 25: 1, 1934.
7. Monserrat, J. L., and Gálvez, I.: Nódulo doloroso de muslo. Tumor glómico (angio- neuro-mioma). *Rév. d. Asoc. méd. argent.* 48: 974, 1934.
8. Aisu, T.: Ein Fall von arteriellem Angiomyoneurom (Masson), *Dermat. Wehnschr.* 99: 1532, 1934.
9. Livingston, W. K.: Tumor of the Subcutaneous Glomus, *West. J. Surg.* 43: 329, 1935.
10. Burman, M. S., and Gold, A. M.: Brief Clinical Study of Glomus Angiomyoneurom. *Artériel of Barré and Masson, New York State J. Med.* 35: 618, 1935.
11. Raisman, V., and Mayer, L.: Tumor of Neuromyo-Arterial Glomus; Cases, *Arch. Surg.* 30: 911, 1935.
12. Stout, A. P.: Tumors of the Neuromyo-Arterial Glomus, *Am. J. Cancer* 24: 255, 1935.
13. Bailey, O. T.: Cutaneous Glomus and Its Tumors; Glomangiomas, *Am. J. Path.* 11: 915, 1935.
14. Chiari, H.: Zur Pathologie der peripheren Gefässe, *Wien. Klin. Wehnschr.* 50: 395, 1937.
15. Kolodny, A.: Glomus Tumor; Glomangioma, *Ann. Surg.* 107: 128, 1938.
16. Popoff, N. W.: The Digital Vascular System, *Arch. Path.* 18: 295, 1934.

PULMONARY CONUS STENOSIS WITH CLOSED FETAL PASSAGES*

REPORT OF A CASE

F. BENJAMIN CARR, M.D., AND HANS LEVI, M.D.
WORCESTER, MASS.

THE following report describes a third case of pulmonary conus stenosis with closed fetal passages. The first two were reported by Eakin and Abbott¹ and by Abbott.²

While the principal structure of the heart to be described is practically the same as in at least one of the cases mentioned, secondary changes and the remarkable duration of life (65 years) seem to warrant this report.

REPORT OF CASE

A 65-year-old, white, married woman came to the Worcester City Hospital, Jan. 13, 1937, complaining of pain in the chest and shortness of breath. She had been in bed practically ever since her previous admission nine weeks before. It was found that she had had several hospital admissions which may be summarized as follows:

Feb. 20, 1933, she was admitted with the diagnosis of grippé. She had felt poorly for a month, with easy fatigability, weakness, palpitation, and cough. These symptoms culminated in her admission to the hospital.

Her past history showed that she had had rheumatic fever at the age of 17 years, since which time she had been known to have "heart disease." She had pneumonia at the age of 34 years. There had been no other illness of note.

The family history was not contributory. She had been married forty-three years and her husband was living and well at the time of her admission. She had one daughter who was in good health at the age of 42 years.

Physical examination was reported as showing a well-developed and nourished white woman. The positive findings were coarse, moist râles at the bases of both lungs, especially the right, with moderate dullness and diminished breath sounds over these areas. The heart was not thought to be enlarged. The sounds were of good quality. The rhythm was normal. There was a loud blowing systolic murmur in the mitral area which was transmitted to the left axilla and heard with less intensity at the aortic and pulmonary areas. The blood pressure was 160/60. The diagnosis at this time was rheumatic heart disease with mitral regurgitation and mild congestive heart failure.

At this admission she was found to have strongly positive blood Hinton and Kahn reactions. Roentgenologic examination showed a very large heart with the apex reaching the left axilla; atheroma was demonstrated in the widened aorta.

There were several subsequent admissions, the only new development being an aortic diastolic murmur. Of chief interest are the various diagnoses made by the different examiners. These were chiefly as follows: arteriosclerotic heart disease with congestive heart failure; syphilis; aneurysm of the aorta; aortic stenosis. At one time one of us left the following note: "probably a calcareous aortic stenosis (with rough basal systolic murmur and thrill)." Some months later our opinion

*From the departments of Cardiology and Pathology, City Hospital, Worcester, Mass.

Received for publication July 25, 1938.

seems to have changed, for we suggest the possibility of congenital heart disease with a patent interventricular septum and an associated syphilitic aortic regurgitation.

Suffice it to say that her final admission occurred on Jan. 13, 1937. During this visit her congestive failure increased regardless of the usual cardiac therapy, and she died Feb. 26, 1937.

Necropsy.—Owing to limitations in the autopsy permission, only a part of the heart was retained, and examination of other organs consisted of inspection only.

The body was that of a well-developed, obese, elderly, white woman, 61.5 inches (153.8 cm.) tall, and weighing 141 pounds (64.1 kg.). The hair was gray. The teeth were in poor condition. There were old striae over the lower abdomen and the upper parts of both thighs. There was marked edema extending from the feet and ankles upward to, and including, the abdominal wall. There was no clubbing of the fingers or toes.

The pericardial cavity was completely obliterated by rather firm, extensive adhesions necessitating the removal of the heart and the pericardium *in toto* by sharp dissection from the surrounding structures.

The heart weighed 530 gm. (from the gross weight of 580 gm., a deduction of 50 gm. was made for adherent pericardium and extrapericardial fat). The coronary arteries showed slight to moderate infiltration with yellow intimal plaques. The walls of all chambers were of good brown-red color, except for a few irregular patches of shiny gray in the lining of both ventricles. The consistency of the myocardium was good. The left ventricle was markedly hypertrophied; its wall measured 2.6 cm. in thickness, while the right ventricle was only slightly hypertrophied, with a wall measuring 0.6 cm. in thickness. The tricuspid valve measured 11 cm. in circumference, the pulmonic 8.5 cm., and the mitral 9.5 cm. All of them were thin and smooth. The leaflets of the pulmonic valve carried thin, long fringes on their corpora arantii. The leaflets of the aortic valve were thickened and contained indurated, partly calcified nodules, but showed no fresh vegetations. They were partly fused with each other, resulting in a decrease of the circumference of the aortic valve to 4 cm. (calcareous aortic stenosis).

The left auricle showed nothing remarkable. The left ventricle, besides the muscular hypertrophy, showed an aneurysm-like pouch extending from the aortic vestibule towards the anterior leaflet of the tricuspid valve (Fig. 1). The entrance to this pouch was oval, measured 0.8 by 0.6 cm., and was located 1.1 cm. below the free edge of the aortic valve. The body of this pouch was slightly wider than its entrance and was lined by several thin, fibrous ridges. Its floor was located 0.5 cm. from the entrance, was found to be flush with the corresponding part of the tricuspid valve, and was smooth and extremely thin. On the right side of the heart, the pouch was located about 0.4 cm. above the attachment of the tricuspid valve, in the auricle. The right auricle was markedly dilated. The foramen ovale was closed.

The right ventricle was subdivided into two separate chambers. One of these chambers was located near the apex of the heart, without quite reaching it, and comprised what may be called the body of the right ventricle. The second chamber was located to the left of, and above, the first. It gradually tapered down from the size of the ventricular body to that of the pulmonary artery. However, a continuation of this second chamber consisted of a pyramidal, muscular structure on the anterior aspect of the heart, extending its lumen 4 cm. towards the right auricular appendage and touching it without communication.

The two chambers were separated by a transverse, fibromuscular septum located about 3 cm. below the attachment of the pulmonic valve (Fig. 2). The periphery of the septum consisted of thick muscles continuous with those of the ventricular wall. Its center was formed by a fibrous plate measuring about 1.5 cm. in diameter

and continuous with one leaflet of the tricuspid valve, with a perforation in the middle. The perforation was an oval, almost slitlike opening which admitted the tip of the little finger and measured 3 cm. in circumference (diameters: 1.3 and 0.8 cm.). Its free edges were thin and beset with thin fringes similar to those found at the pulmonary cusps; some were as long as 0.4 cm. The wall of the ventricular body (first chamber) showed thick trabeculae carneae and a normal moderator band. Apparently there was thickening, in patches, of the endocardium throughout this chamber. The upper chamber showed a smooth, grayish-brown lining uninterrupted by muscular ridges in its main part, but showing a few muscular elevations in its continuation described.



Fig. 1.—Looking down on aortic valve showing deformity of aortic leaflets and sealed interventricular defect and aneurysm.

The aorta showed little, if any, dextroposition. The thoracic portion had a circumference of 9 cm. in the ascending part, of 7 cm. in the arch, and of 6 cm. in the descending part. It showed marked infiltration with yellow intimal plaques and some calcification. Several areas showed patchy separation of calcified portions. Vestiges of the ductus arteriosus were not found, nor any anomaly of the branches of aorta or pulmonary artery.

Anatomic diagnosis was as follows: Pulmonary conus stenosis with closed fetal passages, congenital; calcareous aortic stenosis; acute adhesive pericarditis; aneurysm of membranous portions of interventricular septum; arteriosclerosis of aorta, marked, of coronary arteries, slight; peripheral edema.

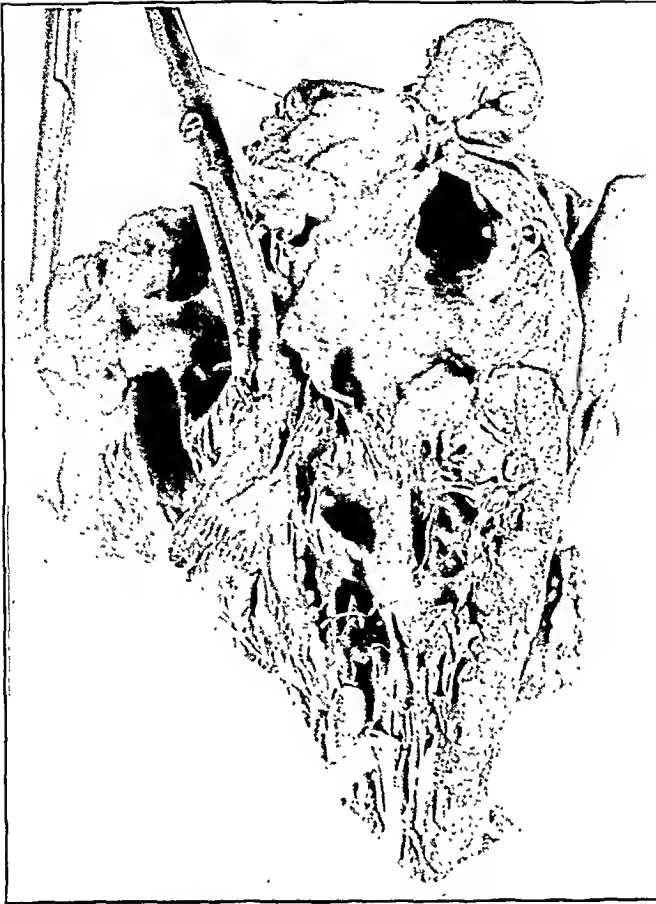


Fig. 2.—View from apex of right ventricle showing stenosis of the pulmonary conus from below.

DISCUSSION

From the standpoint of purely descriptive anatomy, this is an example of constriction of the right ventricle by an incomplete transverse fibromuscular septum. As it obstructed the blood stream directed toward the pulmonary valve, it may be called a subpulmonary stenosis, in analogy to subaortic stenosis, both conditions being of no apparent vital importance unless they are extremely marked or complicated by other cardiac lesions.

Consideration of the homology of this abnormal structure leads one to a normally insignificant feature of the right ventricle, the crista supraventricularis. This is a ridge which marks off the conus arteriosus on the inner wall of the right ventricle. Ontogenetically, it corresponds to a constriction which, in the fourth and fifth weeks of embryonal life, separates the bulbus cordis from the common ventricle.

In our specimen, which is similar to the two referred to above, the upper chamber corresponds to the conus arteriosus in size, location, and the smooth appearance of its lining, whereas the lower chamber is characterized, as is the body of the ventricle, by its muscular relief.

It therefore seems to be obvious that the perforated intraventricular septum represents an arrest of the normal regression of an early embryonal structure to its vestige, the crista supraventricularis. This arrest results in what Eakins and Abbott call, very appropriately, pulmonary conus stenosis. As in their cases, so in ours, the formation of the interventricular septum had been completed, in contrast to the defect of the interventricular wall usually found in pulmonary conus stenosis. As a result of the complete closure of the entire cardiac system of fetal passages, all blood has to pass through the stenotic lower orifice of the conus. However, the relatively moderate size of this opening in our case seems to be the reason for the slight pulmonary congestion and the failure of the systemic circulation. It also explains why this patient lived a fairly normal life until her seventh decade, when the secondary diseases of the left side of the heart and the adhesive pericarditis made the condition incompatible with life.

Another similarity to the formation of the heart in Eakins and Abbott's case number one lies in the presence of a cardiac aneurysm. Such aneurysm deserves particular consideration: Is its floor the result of normal progression in the formation of the interventricular septum, irrespective of the obstacle to the course of the blood from the right to the left side of the heart which it represents? Or is it the result of an endocarditis which, during fetal or extrauterine life, sealed a previously fairly beneficial arteriovenous shunt through the incomplete interventricular septum? We cannot decide this question.

SUMMARY

1. A 65-year-old woman with heart disease, who had begun to have congestive heart failure in Feb., 1933, required repeated hospitalization because of congestive failure until her death four years later. The essential findings in the heart at her last admission were a loud systolic murmur best heard at the second and third left intercostal spaces, accompanied by a thrill, and followed by a moderately loud aortic diastolic murmur. There was no unusual amount of cyanosis and no clubbing of the fingers or toes. The diagnosis was rendered difficult by the history of rheumatic fever, the moderate hypertension, and the positive Hinton and Kahn reactions, as well as the fact that she was at the age when arteriosclerosis could be a prominent factor. She was finally thought to have congenital heart disease, probably with an interventricular septal defect, and syphilitic aortic regurgitation. It must be mentioned that calcareous aortic stenosis was strongly considered, but was second choice.

2. A partial autopsy showed an incomplete, fibromuscular, *intraventricular* septum at the junction of the pulmonary conus and the body of the right ventricle (pulmonary conus stenosis). The *inter-*

ventricular septum was complete, but was covered with thickened endocardium in the form of a small aneurysm. All the fetal passages were closed. The free edges of the intraventricular septum, as well as the pulmonary, tricuspid, and mitral valves, were free from secondary disease. The aortic valve showed a calcareous stenosis. There was acute adhesive pericarditis.

3. The anomaly of the right side of the heart is considered as a congenital malformation consisting of arrest of the process of separation between the pulmonary conus and the body of the right ventricle with subsequent complete closure of the interventricular septum. The manner and time of the closure of the interventricular septum are not determined. Possible causes of an aneurysm in the interventricular septum and its effects upon the circulation are mentioned.

REFERENCES

1. Eakin, W. W., and Abbott, M. E.: Stenosis of Pulmonary Conus at Lower Bulbar Orifice (Conus a Separate Chamber) and Closed Interventricular Septum, With Two Illustrative Cases: Case 1, With Dextroposition of Aorta and Aneurysm of Interventricular Septum, All Fetal Passages Closed; Case 2, With Patent Foramen Ovale and Subacute Infective Endocarditis, *Am. J. M. Sc.* 186: 860, 1933.
2. Abbott, M. E.: *Atlas Congenital Cardiac Disease*, New York, 1936, American Heart Association.

TRUE COR BILOCULARE IN IDENTICAL TWINS

FRANK X. GIUSTRA, M.D.,* AND VINCENT G. TOSTI, M.D.
NEW YORK, N. Y.

TRUE cor biloculare is a grave anomaly of rare occurrence. Some fourteen cases have been reported, nine of which were analyzed by Maude E. Abbott. In nine of the fourteen cases cor biloculare was the primary lesion, but in five instances this lesion complicated other defects. The most commonly associated anomaly was one of the vessels, usually a persistent truncus.

REPORT OF CASES

Baby boy F ("A"), who weighed 2280 gm. and was 46 cm. in length, was delivered by breech extraction. Baby boy F ("B"), who weighed 2820 gm., was 52 cm. in length and was delivered spontaneously and normally.

Two placentas were expressed, connected by membranes. The septum between them was thick and could not be separated. The membranes could be separated easily. There was no connection between the circulations of the placentas. There were no cord anomalies.

The mother had had two previous pregnancies, both uneventful. One child is 3 years of age, the other 11 months of age, and both are well. There was no history of rheumatism, tuberculosis, or heart disease; neither was there a history of any infectious disease at the time of delivery. The mother's blood Wassermann reaction was negative. Her stay in the hospital was uncomplicated by illness.

The physical condition of the twins at birth seemed good. They both cried well and their color was good. However, because baby "A" was underweight, he required special treatment as a premature infant.

A complete physical examination was delayed until approximately ten hours after birth. Baby "A," the smaller and weaker of the two, had a systolic murmur which was heard over the entire precordium. No definite cardiac enlargement could be made out. About thirty hours after delivery, this smaller baby suddenly became cyanotic and dyspneic. The heart sounds were feeble; a systolic murmur was still heard over the entire precordium. The child lived only about five minutes after the cyanosis and dyspnea were first noticed. At autopsy, the heart measured 5 by 3.5 by 2.5 cm. and weighed 18 gm. It consisted of one auricle and one ventricle, separated by a tricuspid valve. Both chambers were dilated. The ventricle led into a large vessel, at the beginning of which was a tricuspid valve. This vessel gave off two pulmonary arteries and then formed a normal aorta with normal branches. The lungs presented many atelectatic areas.

At about the same time that baby "A" died, baby "B" developed an ashen cyanosis and dyspnea. However, his heart sounds appeared to be good and no murmurs were heard. A roentgenogram was taken immediately and revealed an enlarged heart, globular in shape. There was a progressive increase in dyspnea and cyanosis, but still no cardiac murmur. This second child died nine hours after his twin brother. At autopsy, the heart was dilated, measuring 4 by 3.5 by 3 cm., and weighed 18 gm. It consisted of only two chambers, one auricle and one ventricle, between which was a tricuspid valve. The ventricle opened into a vessel guarded by a tricuspid semilunar valve. This vessel gave off two pulmonary arteries and then continued as a normal aorta with normal branches. The lungs presented a few atelectatic areas.

*From the Department of Pediatrics, Long Island College Hospital and Long Island College of Medicine; Dr. Charles A. Weymuller, director.

Received for publication Aug. 14, 1938.

The complete autopsies revealed no other congenital defects or evidence of other disease in either infant.

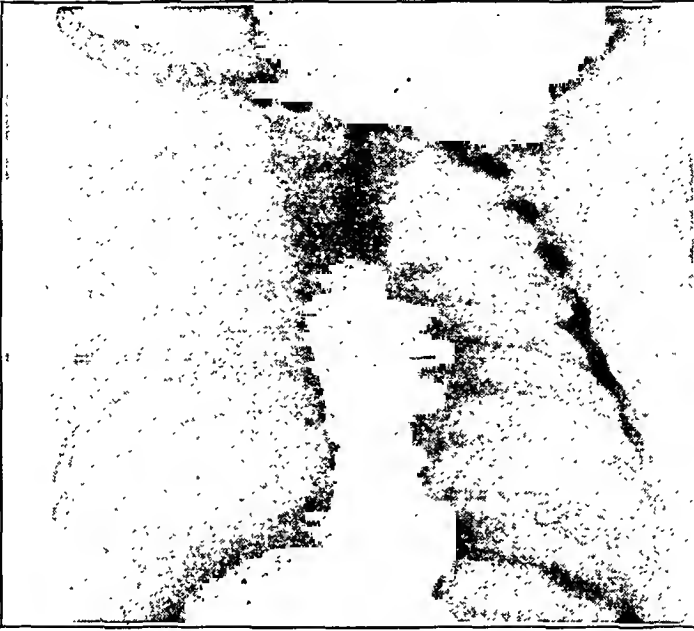


Fig. 1.—Roentgenogram of Baby "B."

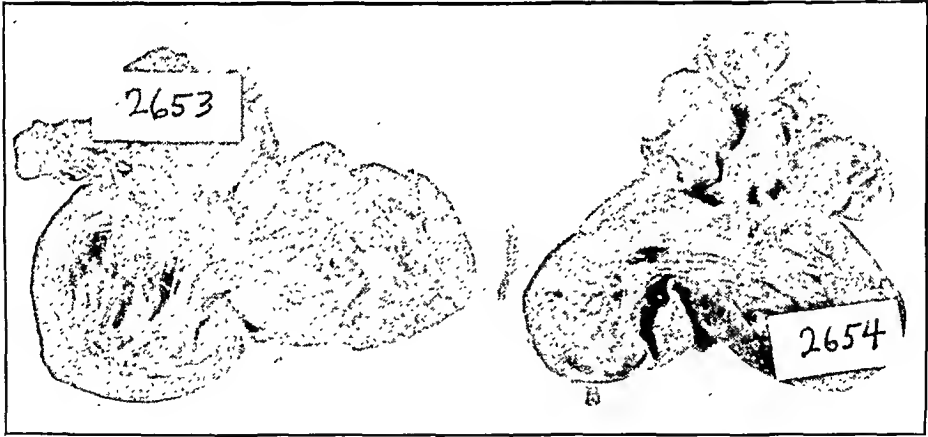


Fig. 2.—Identical double-chambered hearts of the twins. The heart on the left is photographed to show the auricle and ventricle and tricuspid valve, while that on the right is arranged to show the valve and ventricle and the efferent artery in which two pulmonary orifices are visible.

SUMMARY AND CONCLUSIONS

Twin babies who weighed 2280 and 2820 gm. succumbed to identical congenital lesions of the heart and vessels approximately 30 hours and 39 hours, respectively, after birth. The lesion of the heart was true cor biloculare, and the associated anomaly was a persistent truncus.

These cases are reported because our search of the literature has failed to disclose any similar instance in which identical twins suffered from cor biloculare with persistent truncus.

Department of Reviews and Abstracts

Selected Abstracts

Strong, Kenneth C.: A Study of the Structure of the Media of the Distributing Arteries by the Method of Microdissection. *Anatomical Record* 72: 151, 1938.

Microdissection studies of the arteries of a number of animal species reveal the media to be composed of compact, concentric laminae of obliquely directed, fusiform muscle cells united so closely as to suggest a syncytial character. The cells are organized into a continuous spiral structure.

The functional significance of the organization of the arterial muscle into a continuous spiral structure is discussed. The studies suggest the possibility of distributing arteries contributing to the forward movement of the blood by their intrinsic motor activity.

Illustrations of the continuous spiral structure of arterial muscle are contained in two plates.

Segal, Harry L.: Cigarette Smoking. *Am. J. M. Sc.* 196: 851, 1938.

Cigarette smoking can be the cause of fatigue in some people and this fatigue can be relieved by stopping cigarette smoking.

Cigarette smoking produces definite changes in the electrocardiogram, mainly: (1) an increase in the heart rate; (2) a lowering of the T-wave.

Both standard and the so-called denicotinized brands produce the same effects.

Although the filter-holders described decrease the amount of nicotine in cigarette smoke, a sufficient amount of nicotine is still available to produce the above changes in the electrocardiogram.

These effects occur mainly in people under 50 years of age.

AUTHOR.

Moia, B.: A Study of the Ventricular Complex in Electrocardiograms With Left Axis Deviation. *Rev. argent. de cardiol.* 5: 75, 1938.

A total of 338 electrocardiograms showing left axis deviation (deep S_{III} , R_I greater than R_{III} , the entire QRS complex lasting no longer than ten seconds) were analyzed. They were obtained from 316 ambulatory patients submitted to complete cardiovascular studies. They fell into four groups:

1. R_s small, S_s deep, 222 records (60.22 per cent). In 102 there was no S_T wave; of these 13.72 per cent had S-T changes in all leads (low in 182, high in 3) and 11.76 per cent had negative T_I . There was no clinical evidence of heart disease in 17.69 per cent.

In 122, S_s waves were marked; of these 13.10 per cent had S-T changes as noted above and 11.40 per cent negative T_I . There was no clinical evidence of heart disease in 8.83 per cent.

2. S_s preceded and followed by small positive peaks (triphasic QRS), 64 cases (18.93 per cent). Of these 6.50 per cent had S-T changes, and as many had inverted T_I waves. In 18.7 per cent no evidence of heart disease was shown.

3. Deep Q_s with or without subsequent S-wave. Twenty-eight records, or 8.28 per cent of these, 21.43 per cent had marked S-T changes, and 14 per cent negative T_I . Of these, 25 per cent had no evidence of clinical heart disease.

4. M- or W-shaped QRS₂, 22 records (6.50 per cent). None of these showed changes of the S-T segment or T-wave changes. No evidence of heart disease was shown in 22.78 per cent.

All of the patients without demonstrable heart lesions had involved T₂ waves, except one patient in Group 1B and two in Group 3. With left axis deviation, therefore, an upright T₂ is almost certainly pathologic. Also in borderline cases there was a marked tendency for T₂ to be inverted.

Changes in the S-T segment (lowered in Leads I and II, elevated in Lead III) and inverted T-waves in Leads I and II, are almost certainly pathologic in cases of left axis deviation.

In left axis deviation an S₂ with a low N₂ or a low R₂, whether it is notched or sharp, usually indicates severe myocardial damage though not always coronary disease.

JENSEN.

Russafiea, Adriana, and Puddu, Vittorio: The Action of Digitalis on the Pre-cordial Lead of the Electrocardiogram. *Cuore e circolaz.* 22: 453, 1938.

A total of 24 cases (21 normal and 3 cardiac) free from digitalis for at least three weeks were given 0.5 gm. of digitalis daily for four to six days. The chest leads were taken with the technique accepted by the American Heart Association. Most commonly the digitalis was followed by complete inversion of the T-waves, sometimes without corresponding change in the standard leads. In some cases the S-T segment was changed so as to simulate the precordial lead of infarction of the posterior wall; none in this series simulated infarction of the anterior wall.

JENSEN.

Hartog, H. A.: Bundle Branch Block With Short P-R Interval in Electrocardiogram From People With Organic Heart Disease. *Nederl. tijdschr. v. geneesk.* 82: 5112, 1938.

In a series of four cases of bundle branch block and short P-R interval, the lesion is explained by accelerated A-V conduction rather than by block. One case had also mitral stenosis. There is excellent reproduction of the four electrocardiograms.

JENSEN.

Martin, S. J., and Gorham, L. W.: Cardiac Pain. *Arch. Int. Med.* 62: 840, 1938.

An attempt has been made to determine the role of the mechanical factor in the initiation of cardiac pain in dogs recovering from anesthesia. It has been found that a typical pain in response can be elicited when tridirectional tension in one plane is applied to a coronary vessel in such a manner as to cause no change in blood flow. With this procedure the chemical factors caused by impaired coronary blood flow are completely eliminated, as shown by the absence of changes in the electrocardiogram. The minimal threshold of tension on ligatures in the coronary vessel was 3 gm. in the series of dogs used. Local application of alcohol can block stimuli initiating cardiac pain, whether mechanical or chemical in origin. It is concluded that tension alone on the coronary arteries in dogs may serve as an adequate stimulus for the initiation of cardiac pain.

AUTHORS.

Heim de Balsac, R.: Parietal Aneurysm of the Heart. *Leçons de Cardiologie faites à l'hôpital Broussais* 2: 185, 1938.

This is a fine summary of the subject comparable to that by Parkinson, Bedford, and Thomson in London. It is well illustrated both with pictures and case reports. In almost all cases the aneurysm results from myomalacia following coro-

nary occlusion, though the history of this is often vague. Only 2 to 5 per cent are on a syphilitic basis (gumma). Two-thirds of the patients are men between the ages of 40 and 60 years. Usually the descending branch of the left coronary is affected. The left ventricle is almost exclusively affected. Some aneurysms cause thinning of the cardiac wall only, without change in the external contour of the heart. Such a case is illustrated with contrast medium placed post mortem in the ventricle. The mechanics of the area is shown in a preparation with injected cardiac vessels. Cardiac aneurysms may be multiple. Physical signs are variable and unreliable; the more important ones are discussed in detail. Until the days of systemic fluoroscopy the diagnosis was rarely made during life. Also the electrocardiographic findings are mostly those of various forms of myocardial damage. Many aneurysms can be seen deforming the left border, either as hemispherical prominences or rendering the outline of the rectangular shadow. When paradoxical pulsation is discovered it is an important sign; it tends to disappear later in the course of the disease. In late cases the movements follow those of the ventricular wall but are somewhat delayed, "postsystolic."

Cardiac aneurysms rarely rupture; this accident usually occurs in the acute stages of occlusion. The aneurysm seems to form in the course of three to six weeks. In itself, it has a good prognosis really constituting a form of healing after occlusion, but it is so often associated with serious coronary diseases that the prognosis is determined by this factor.

Taken together, the English and this French paper admirably cover the subject. Both are accompanied by extensive bibliographies which curiously seem to be drawn from widely different sources.

JENSEN.

Puddu, Vittorio: Clinical and Electrocardiographic Observations on 30 Cases of Infarction of the Myocardium. *Minerva Med.* 2: 9, 1938.

This is a nice study of thirty cases of chief interest to readers not familiar with the condition and to those collecting series for mass analysis. It is well arranged and has illustrations of considerable didactic interest. Twenty cases were diagnosed during life, two at autopsy, twenty-eight were males and two were females. The youngest was 31 years of age, the oldest, 74 years. Six had syphilis. Special attention is given to prodromal symptoms and symptomatic cases. The value of precordial leads is demonstrated. Of eight cases observed in the attack, two died. Of thirty references to the literature, twenty-two are from American sources.

JENSEN.

Gorham, L. W., and Martin, S. J.: Coronary Occlusion With and Without Pain. *Arch. Int. Med.* 62: 821, 1938.

A study of the clinical histories and necropsy data for 100 patients with proved coronary occlusion showed that 58 had cardiac pain and 42 did not, indicating a higher frequency of painless occlusion than is generally recognized.

The following broad statement may be made regarding Group 1, comprising 58 patients who suffered from cardiac pain in a fatal attack: The patients tend to be younger; males show the peak mortality ten years earlier than do females; a history of preceding attacks of anginal pain and of hypertension is more common; pain overshadows dyspnea as a symptom, and a pericardial friction rub is much more often heard. Actual thrombosis, acute infarction, acute pericarditis, and milder grades of coronary sclerosis are more frequently encountered than in the patients in Group 2. The location of the infarct and the rupture of the ventricle, with resulting hemopericardium, bear no relation to pain.

The following general statement may be made regarding Group 2, comprising 42 patients who had no pain in a fatal attack of coronary occlusion: The patients tend to be older than those in Group 1; the peak mortality is shown to be a decade earlier than in females; a history of preceding attacks of anginal pain and of hypertension is less common; dyspnea is generally an outstanding symptom, and a pericardial friction rub is rarely heard. Old infarcts, with absence of actual thrombosis and pericarditis, are more frequent. Marked sclerosis of the coronary arteries is slightly, though not significantly, more often encountered. The location of the infarct and the rupture of the ventricular wall, with resulting hemo-pericardium, bear no direct relation to the absence of pain.

A combination of actual thrombosis of the coronary artery and acute infarction was accompanied by pain in every one of the 15 instances in which these two factors were present. A combination of fibrotic narrowing of a coronary artery, without actual thrombosis, plus old infarction and absence of pericarditis, was not accompanied by pain in 12 of 17 patients (70 per cent). All the 5 patients who did have pain suffered only from a slight degree of it; dyspnea was the dominant symptom in 4 of these cases.

The old mechanical theory of cardiac pain advocated by Allbutt and Wenckebach and more recently advocated by Herrmann, which has been generally discarded in favor of Lewis' theory of ischemia, has been re-examined in the light of our study, and the role of a tension in coronary occlusion varies directly with the speed with which increased tension is produced on the wall of the coronary artery proximal to the obstruction and with the pathologic changes in the wall, whether these changes are due to a reduced elasticity or an actual degeneration of the sensory nerves.

The tension factor seems to offer a reasonable explanation, not only for the presence, but for the absence of pain in cases of coronary occlusion.

Added support for the importance of the factor of tension in the production of cardiac pain has been obtained by an experimental study on animals, the results of which are recorded in a separate communication.

AUTHORS.

Brill, I. C.: *Coronary Artery Disease and Angina Pectoris; The Present Status With a Review of Some of the Recent Literature.* Ann. Int. Med. 12: 365, 1938.

The author has condensed into a single paper a readable summary of the accumulated information upon this vital and increasingly important subject.

MCCULLOCH.

Routier, D., and Heim de Balsac, R.: *Six Clinical Observations on Congenital Cardiac Malformation of the Type Called "Communication Interauricular."* Bull. Soc. belge de Cardiologie, January, 1938.

A study based on the observation of six cases of this anomaly; all were females; two were cyanosed, a fact attributed to some concomitant lesion; symptoms were slight.

Auscultation: A diastolic murmur can be heard over the second arch on the left border, often also a systolic murmur, but without the peripheral signs of the aortic lesion. The diastolic murmur is probably produced by eddies in the dilated pulmonary artery.

X-rays: Marked prominence of the second arch; marked ventricular mass with apex rounded but not submerged below the dome of the diaphragm. Prominent right border; aortic arch hardly visible.

Electrocardiogram: Right axis deviation and marked notching of QRS.

These cases differ from ones of persistent ductus arteriosus by the prominence of the right border and the smallness of the aortic arch.

JENSEN.

Coburn, Alvin F., and Pauli, Ruth H.: A Precipitinogen in the Serum Prior to the Onset of Acute Rheumatism. J. Exper. Med. 69: 143, 1939.

A precipitin reaction occurs between sera taken just before and shortly after the onset of acute rheumatism. It is clear that the reaction is distinct from the precipitation of pneumococcus C substance and of certain of the streptococcus antigens. It is, of course, possible that the phenomenon observed does not represent an antigen-antibody reaction.

Whatever its nature may prove to be, as a working hypothesis this precipitinogen may be considered either a primary or secondary antigen. Its absence in sera taken during phase I and its late appearance in phase II would seem to be against its direct bacterial origin, although this cannot be excluded. Another possibility is a secondary antigen such as the precipitinogen described by Hughes in yellow fever. It has been shown that in rheumatic subjects who develop acute rheumatism, the appearance of circulating antibodies to hemolytic streptococcus is characteristically late. During this delay streptococcal products are presumably free to react with human tissue constituents. Such an interaction might result in the precipitinogen with which we are dealing.

AUTHORS.

Leverton, W. R.: The Heart in Pulmonary Tuberculosis; Electrocardiographic Consideration. Ann. Int. Med. 12: 285, 1938.

A study was made of 416 cases of active pulmonary tuberculosis and 44 inactive cases. The cases were classified according to anatomic position of the heart; 47 showed shift of the heart to the right, 119 to the left, and 250 no shift of heart.

Arterial hypertension was found in 38 of the active cases, but not in any of the inactive cases.

One hundred and eighty-nine, or 45.5 per cent, of the total number of active cases studied showed significant changes in the QRS complex, the RST segment, or the T-wave. None of the inactive cases showed any important abnormality of the electrocardiogram.

There were 19 graphic records which showed an abnormal Q-wave; 12 of these were of the Q_s type described by Pardee. Thirty cases showed intraventricular block, 43 abnormality of the RST segment, and 119 abnormal T-waves.

The electrical axis is apparently influenced by the rotation of the heart on its longitudinal axis.

The percentage of cases showing an increase in the duration of the QRS depression and elevation of the RST with T-wave changes is higher than expected and suggests that the nutritional disturbance of the myocardium found in pulmonary tuberculosis of long standing may produce an electrocardiographic picture similar to that found in coronary disease.

The electrocardiogram is of value in the diagnosis of cardiac lesions associated with pulmonary tuberculosis. It is frequently the only positive evidence of myocardial disturbance.

AUTHOR.

Ayman, David, and Goldshine, Archie D.: Cold as a Standard Stimulus of Blood Pressure. *New England J. Med.* 219: 650, 1938.

The literature describing the use of the cold-pressor test of Hines and Brown is critically reviewed. No study was found that had repeated the same technique as that of Hines and Brown in a group of patients with essential hypertension. The test, using the exact technique of Hines and Brown, was repeated in forty-eight subjects with normal blood pressure and eighty-eight subjects with essential hypertension. The results were in close agreement with those of Hines and Brown.

The final significance of the excessive reactions in certain people with normal blood pressure will be known only after these subjects have been followed for a number of years in order to note how many develop true essential hypertension. For the present, the value of the cold test appears to lie in the field of investigation rather than in that of practical application. It is possible, however, that it will eventually prove of real value in general practice to pick out many future candidates for essential hypertension or hypertension during pregnancy or those with past hypertension.

NAIDE.

Rothstadt, L. E.: The Effect of Auricular Fibrillation on the Course of Hypertension. *M. J. Australia* 1: 813, 1938.

The frequency of auricular fibrillation in 1,000 cases of hypertension uncomplicated by mitral stenosis was 7.3 per cent.

Hypertension uncomplicated by mitral stenosis was present in 49 (or 11.2 per cent) of 435 cases of auricular fibrillation.

Hypertension uncomplicated by mitral stenosis was present in 32 (or 33.7 per cent) of 95 patients who had had paroxysms of auricular fibrillation.

A study was made of 50 patients with hypertension and established auricular fibrillation. All were between 45 and 75 years of age. Auricular fibrillation is commoner in older than in younger patients with hypertension.

The radiologic appearances are described and the difficulties in interpretation are discussed.

Congestive heart failure and embolism were common sequelae.

The response to treatment was variable. Eighty per cent of the deaths occurred within two years of the onset of fibrillation; but with treatment a patient might live for several years.

Post-mortem appearances in seven patients are described.

Thirty-six patients with hypertension and paroxysmal auricular fibrillation were studied.

The prognosis in hypertension with paroxysmal fibrillation is better than in hypertension with established fibrillation, other things being equal.

Quinidine therapy often reduces the frequency of, or abolishes, the paroxysms.

AUTHOR.

Kunkel, Paul, and Stead, Eugene A., Jr.: Blood Flow and Vasomotor Reactions in the Foot in Health, in Arteriosclerosis, and in Thromboangiitis Obliterans. *J. Clin. Investigation* 17: 715, 1938.

Measurements of the blood flow in the foot in health, in arteriosclerosis, and in thromboangiitis obliterans were made under standard conditions by the plethysmographic method. The flow was recorded as cubic centimeters of blood per minute per 100 c.c. of tissue.

The blood flow to the foot reached a constant level after thirty minutes at 43° C. The flow at this temperature has been designated as the "maximal" flow.

The average maximal blood flow to the foot in normal persons was 17.1 c.c., with the highest 25.9 and the lowest 11.1 c.c. Ninety per cent of the flows were

between 13 and 20 c.e. The average difference in the maximal flow in the right and the left foot was 1.8 c.e.

The maximal blood flow in the foot showed no appreciable decrease with age (17 to 67 years) in the presence of normal cardiovascular system.

The average maximal blood flow in the hand per equal volume of tissue was twice that in the foot. When calculated in relation to skin area the maximal flow in the hand was 30 per cent greater than that in the foot.

The vasomotor reactions of the hand and foot were qualitatively similar. The rhythmic respiratory waves observed during normal breathing resulted from the changes in venous pressure associated with respiration and were not of vasomotor origin. A deep inspiration, however, induced constriction of vasomotor origin in both the hand and the foot.

In arteriosclerosis and thromboangiitis obliterans the maximal blood flow to the foot was reduced 50 per cent without symptoms or trophic disturbances. When the flow was reduced to one-third the normal value, or to the level of 5 c.e. or below, symptoms or trophic disturbances usually occurred.

In both arteriosclerosis and thromboangiitis obliterans severe intermittent claudication in the calf was in some cases incapacitating, though the blood flow in the foot was as great as in many normal individuals. Thus the presence of an adequate supply of blood to the foot did not eliminate the possibility of obliterative disease involving the vessels of the calf muscles.

AUTHORS.

Thomas, K. Jefferson, Cohen, Mandel E., and Hamilton, Burton E.: Studies on the Circulation in Pregnancy. *Am. J. M. Sc.* 196: 819, 1938.

Lead V of the electrocardiogram was determined 398 times on 288 pregnant women.

The T-wave was observed to be upright in 7.7 per cent of normal pregnant women.

Changes in the chest lead during pregnancy, particularly those in the T-wave, were thought to be associated with changes in the position of the heart.

Lead V is of no particular value in diagnosis of heart disease during pregnancy.

Recognition of normal variation in Lead V of the electrocardiogram during pregnancy will avoid erroneous diagnoses of myocardial disease in pregnant women with normal hearts.

These conclusions apply only to chest leads taken with the electrodes placed in the manner described above (i.e., exploring electrode in the fourth interspace 5 cm. to the left of the sternum, indifferent electrode on left leg) and do not apply necessarily to chest leads taken with the exploring electrode at the apex of the heart.

AUTHORS.

Routier, D., and Heim de Balsac, R.: Modification of the Trachea and Bronchi in Mitral Disease. *Arch. d. mal. du coeur.* 30: 861, 1937.

By injecting a small amount of lipiodol, the authors brought into clear relief the larger bronchi and showed how enlargement of the left auricle changed their course; first the angle between the bronchi is widened and the left bronchus tends to wind a more horizontal course. Then their course becomes curved to embrace the enlarged auricle "like the legs of a rider gripping the horse." Enlargement of the right auricle does not affect the bronchi, but in cases of large pulmonary arteries, the bronchi may become compressed and the angle between them may become lessened from pressure by these vessels.

JENSEN.

American Heart Association, Inc.

RADIO CITY

50 WEST 50TH STREET, NEW YORK, N. Y.

DR. WILLIAM J. KERR
President

DR. WILLIAM D. STROUD
Vice-President

DR. HOWARD B. SPRAGUE
Secretary

DR. WALTER W. HAMBURGER
Treasurer

BOARD OF DIRECTORS

DR. T. HOMER COFFEN	Portland, Ore.	DR. STEWART R. ROBERTS	Atlanta
DR. CLARENCE DE LA CHAPELLE	New York City	DR. WILLIAM H. ROBEY	Boston
DR. WALTER W. HAMBURGER	Chicago	DR. ROY W. SCOTT	Cleveland
DR. GEORGE R. HERRMANN	Galveston	*DR. HOWARD B. SPRAGUE	Boston
DR. EMMET F. HORINE	Louisville	*DR. WILLIAM D. STROUD	Philadelphia
*DR. WILLIAM J. KERR	San Francisco	DR. LOUIS VIKO	Salt Lake City
*DR. EMANUEL LIBMAN	New York City	DR. HOWARD F. WEST	Los Angeles
DR. HUGH MCCULLOCH	St. Louis	DR. PAUL D. WHITE	Boston
*DR. GILBERT MARQUARDT	Chicago	DR. FRANK N. WILSON	Ann Arbor
*DR. H. M. MARVIN	New Haven	DR. CHARLES C. WOLFERTH	Philadelphia
*DR. EDWIN P. MAYNARD, JR.	Brooklyn	*DR. IRVING S. WRIGHT	New York City
DR. JONATHAN MEAKINS	Montreal	*DR. WALLACE M. YATER	Washington, D. C.
*DR. FRANKLIN NUZUM	Santa Barbara		

DR. H. M. MARVIN, *Acting Executive Secretary*

GERTRUDE P. WOOD, *Office Secretary*

TELEPHONE CIRCLE 5-8000

THE American Heart Association, sponsor of the first International Health Broadcast, stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is \$5.00 a year and journal membership at \$10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

**Executive Committee.*

The American Heart Journal

VOL. 17

MARCH, 1939

No. 3

Original Communications

THE EARLIEST KNOWN REFERENCE TO THE HEART AND CIRCULATION

THE EDWIN SMITH SURGICAL PAPYRUS, CIRCA 3,000 B.C.

WALTER W. HAMBURGER, M.D.*
CHICAGO, ILL.

CLAIMS to priority in scientific discovery have long played an important role in the history of biologic knowledge. Controversy and polemics have often been their accompaniment, and in so far as they have stimulated further research they have often served a useful purpose. Cannon has recently stressed the value and harm of scientific controversy.¹ It is generally admitted that virtually all new discoveries in the field of biology have developed step by step from preceding knowledge, a mosaic integrated from countless sources. The evolution of new concepts is the inevitable consummation of ideas previously and widely held by scientific men of many lands, rather than the result of the brilliance of any single investigator. This has been traced by Stern,² particularly in medicine.

In the seventeenth century, Stern found that within a period of two years four different observers from four different countries independently described the intestinal lymphatics and their connection with the thoracic duct. In the field of the circulation, angina pectoris was described practically simultaneously by Rougnon in France and Heberden in London in 1768, while in 1889 both Bouveret in France and Hoffmann in Germany described paroxysmal tachycardia.†

*From the Department of Medicine, with the assistance of the staff of the Oriental Institute, University of Chicago.

Received for publication Aug. 29, 1938.

†B. Ebbell, in his recent translation of the Papyrus Ebers (Oxford University Press, London, 1937), believed that the ancient Egyptian physicians "as good observers had perceived that certain symptoms often occur together, and on this basis they were able to establish various syndromes as pathological unities, for instance angina pectoris (27₁₀₋₁₁)" (page 13). "If thou examinest a man for illness in his cardia, and he has pains in his arm, in his breast (mamima) and in one side of his cardia, and it is said of him: it is w3d — illness, then thou shalt say thereof = it is (due to) something entering into the mouth, it is death that threatens him."

‡Here the reference is presumably to angina pectoris (page 48).

Scientific dispute loses much of its intensity when viewed over the long range of the rise of civilized man, particularly as new discoveries, archeological, anthropological, and paleographic, frequently antedate, perhaps invalidate, previously held views.

Such experiences make for caution and conservatism in the evaluation of priority of discovery in the broad sweep of history and science. The phrase so aptly coined by the distinguished orientalist, James Henry Breasted, "The New Past,"³ takes on ever increasing significance as new and undiscovered material, reaching back to the early dawn of civilized man, is unfolded by continuing archeological study and research. Knowledge and understanding of our common historical heritage gained by intensive archeological field, laboratory, and library investigation will doubtless throw additional light on our present-day concepts, second only to progress and discovery of the unknown future. In other words, one may conceive of research into the broad fields of human understanding through efforts in two diametrically opposite directions: the one into the past (antiquity), rediscovering what our ancestors knew and taught as commonplace; the other into the future, advancing our frontiers of knowledge.

The publication by Haddad and Khairallah, in 1936, of "A Forgotten Chapter in the History of the Circulation of the Blood,"⁴ is pertinent to this discussion. In their paper, the authors present conclusive evidence that the discovery of the pulmonary circulation, long attributed to the theologian-heretic Michael Servetus, in 1553, had been made some three centuries earlier by a prominent Arabian physician, Ibn Nafis, who in three separate manuscripts in the thirteenth century gave a classic description of the lesser circulation. The material on which this conclusion was based is contained in a manuscript in possession of the authors—"Commentary on the Anatomy of the Canon of Avicenna"—in which Ibn Nafis, a student of medicine at Damascus, dean of the Mansoury Hospital, Cairo, Egypt, clearly and repeatedly described the pulmonary circulation.

Caution and care are therefore necessary in any inquiry into priority in a given subject, for which reason this paper has been entitled "The Earliest *Known* Reference to the Heart and Circulation" paralleling Dr. Breasted's reference to the Edwin Smith Surgical Papyrus as the "earliest *known* surgical treatise."

Writings and papers concerning the heart and circulation in antiquity usually start with Hippocrates (460 B.C.), Aristotle (384 to 322 B.C.), and Galen (A.D. 129 to 200), although mention of knowledge and concepts of the heart and circulation are known to be contained in the Ebers Papyrus (2000 to 1500 B.C.).

The present communication contains material largely drawn from the "Edwin Smith Surgical Papyrus" (circa 3000 B.C.*). It makes no claim for originality. Rather, it is a compilation of material accessible to any and all students. Credit for discovering and publishing the material it contains belongs to Edwin Smith, his daughter, the New York Historical Society, Dr. Breasted, and the Oriental Institute.

The history of Edwin Smith, the finding, acquisition, translation, and publication of his papyrus are of considerable interest to Egyptologists, archeologists, and students of medical history and perhaps may best be given in Dr. Breasted's own words:

"Early in the history of the Oriental Institute, Dr. Caroline Ransom Williams, one of our own doctors, then engaged in the study and publication of the Egyptian collection of the New York Historical Society, called the writer's attention to the existence of a large and beautifully written papyrus in a stately ancient book format. . . . This papyrus roll, purchased at Thebes in 1862 by Mr. Edwin Smith, had been given to the New York Historical Society by his daughter in 1906. On examination the papyrus proved to be a surgical treatise. After further study, it was found to be a document of the highest importance in the history of science, being not only the earliest known surgical treatise, but at the same time the earliest document in the history of science."³

"Edwin Smith, after whom the papyrus is named, was born in Connecticut in 1822, the year that witnessed the first decipherment of Egyptian hieroglyphic by Champillon. Smith was one of the earliest students of Egyptian in any country. He studied hieroglyphic in London and Paris when the science was only a quarter of a century old, and was probably the first American to learn scientifically the little then known about the Egyptian language. It is of no little interest to Americans to know that its (the papyrus) discovery goes back to the earliest days of Oriental Science in the United States, and indeed to the first generation of Egyptology anywhere."⁵

DR. BREASTED'S COMMENTS ON THE PAPYRUS

That Dr. Breasted was well aware of the significance and interest of the papyrus to surgeons, physicians, and physiologists is clearly shown in his dedication: "To the memory of William Harvey, discoverer of the circulation of the blood, at the three hundredth anniversary of his great discovery, this publication of the earliest known surgical treatise is dedicated." Without going into a general description of the papyrus

*The present copy of the papyrus dates from the seventeenth century B.C., although the author's original manuscript was produced at least 2,000 years earlier and was written some time in the Pyramid Age (3000 to 2500 B. C.). It may have been written by the earliest known physician, Imhotep—the great architect physician who flourished in the thirtieth century B.C.

(which may be consulted first hand by those interested), one may state briefly that it contains a systematic description of forty-eight cases of injury and disease, probably mostly of soldiers disabled in warfare, with notes of the examination, diagnosis, prognosis, and treatment indicated, in each case, by an "unknown ancient surgeon." I have selected only that material from the papyrus which seemed to have a particular and direct interest to the heart and circulation; it is comprised largely, if not entirely, of Dr. Breasted's own commentaries.

In the foreword (page XVI) Dr. Breasted, in discussing knowledge possessed by "our ancient surgeon," writes as follows:

"He knew of a cardiac system and was surprisingly near recognition of the circulation of the blood, for he was already aware that the heart was the center and the pumping force of a system of distributing vessels. He was already conscious of the importance of the pulse and had probably already begun to count the pulse, a practice heretofore first found among the Greek physicians of the third century B.C. in Alexandria."

In some exceedingly interesting comments on the pulse and its relation to the heart beat and the circulation of the blood, we find the following (General introduction, page 13):

"The importance of observing the action of the heart in determining the condition of a patient appears here for the first time in medical history. The passage containing these observations unfortunately falls in the only broken and fragmentary column in our document, resulting in some uncertainty over the following important point. In spite of the imperfect condition of the text of this passage, there is much probability that the surgeon *counts* the strokes of the pulse, and it is doubtless a significant fact that the first physician who is known to have counted the pulse, Herophilus of Alexandria (born 300 B.C.), lived in Egypt. It will probably also not have been wholly an accident that this was done in the land which produced the earliest known time-pieces, for Herophilus used an Egyptian water-clock for timing the count of the pulse. Herophilus is well known to have been an investigator of much independence, and he was one Greek physician who so nearly approached the discovery of the circulation of the blood, that there are historians of Medicine who believe that he actually achieved this discovery. Before his time, Greek Medicine had been long misled by the dogma that a force resident in the *arteries* caused the pulse. Our treatise, however, already knows that the pulse is due to the force and action of the *heart*. Herophilus was the first *Greek* physician to recognize this fact. That he should have lived in Egypt, where the cardiac system disclosing the *heart* as the central

force had already been known for perhaps 2,500 years is hardly likely to have been a pure coincidence. It should be made quite clear, however, that our treatise, while it shows knowledge that the action of the heart affects and supplies all extremities and all parts of the body with blood, does not indicate a recognition of the *circulation* of the blood."

Dr. Breasted comments on the surgeon's careful examination of a brain injury, and his interpretation of the findings is as follows (page 14): "Our ancient surgeon . . . probes with his fingers to the interior and discovers cardiac pulsations, or as he says the 'fluttering and throbbing like that on the crown of an infant's head before it has grown together.'"

Correlation of the pulse and the heart is seen from the following (page 64): "In observing the pulse, our surgeon knows he is examining the operation of the heart, and he states that the observation of the pulse is undertaken 'in order to know the action of the heart.'"

Further interesting observations on the pulse and its measurement follow (page 105): "When we note that the discussion in the next few lines . . . pictures the physician as placing his hands or fingers at various points along the body of the patient and discerning the pulsations of the heart from one extremity to the other, the question inevitably arises whether he is not discussing the counting of the pulse in making these references to . . . 'counting.' If so, it is the earliest such reference in the history of medicine, for the counting of the pulse was unknown to early Greek Medicine and is not mentioned until Democritus and the Hippocratic treatises.

"It first occurs in the treatise *peri trophēs* about 400 B.C. It would be of especial interest as occurring at this remote age, not only in the history of physiology, but also in the history of the development of instruments for time measurement; for it would be impossible to count the pulse without an instrument finely enough developed to measure *small* intervals of time. The Egyptian water clocks or shadow clocks now known to us would have been rather ill suited for use in accurate counting of the pulse beat. The physician would have needed a portable time measure. . . . The earliest known counting of the pulse with a time measure was done by the distinguished Herophilus of Alexandria in the third century B.C."

THE PAPYRUS

Turning now to examine the facsimile of the papyrus itself, we see in Fig. 1 a photograph of the facsimile of Column I of the surgical treatise, dealing with three cases of head wounds, written in hieratic.

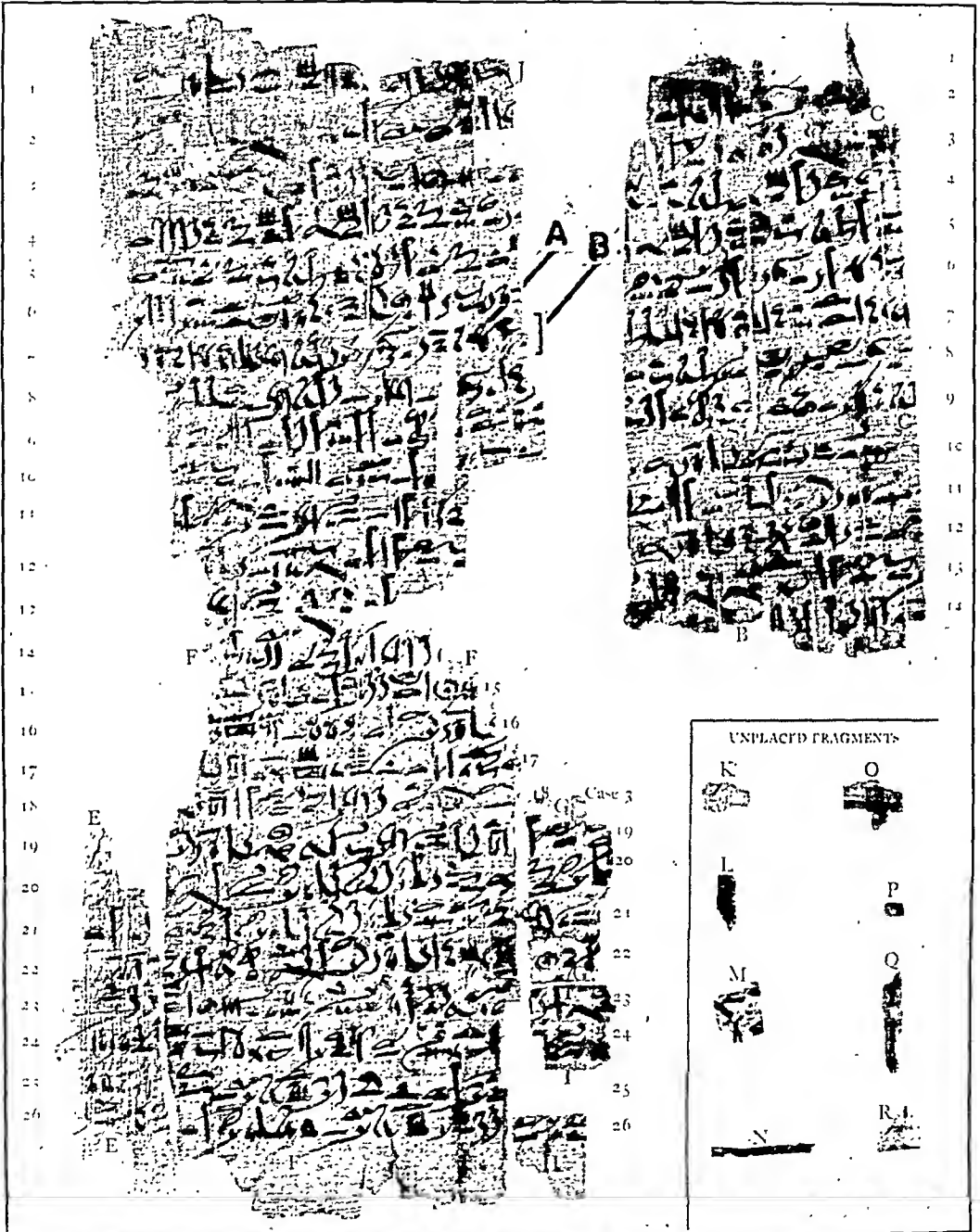


Fig. 1.—Photograph of the facsimile of Column I of the Surgical Treatise dealing with three cases with head wounds (Edwin Smith Surgical Papyrus. New York Historical Society.) A, Sense sign (ideogram) for the word "heart"; B, sound signs (phonograms) for the word "heart" (hieratic). University of Chicago Oriental Institute Publications. University of Chicago Press, Chicago, 1930.

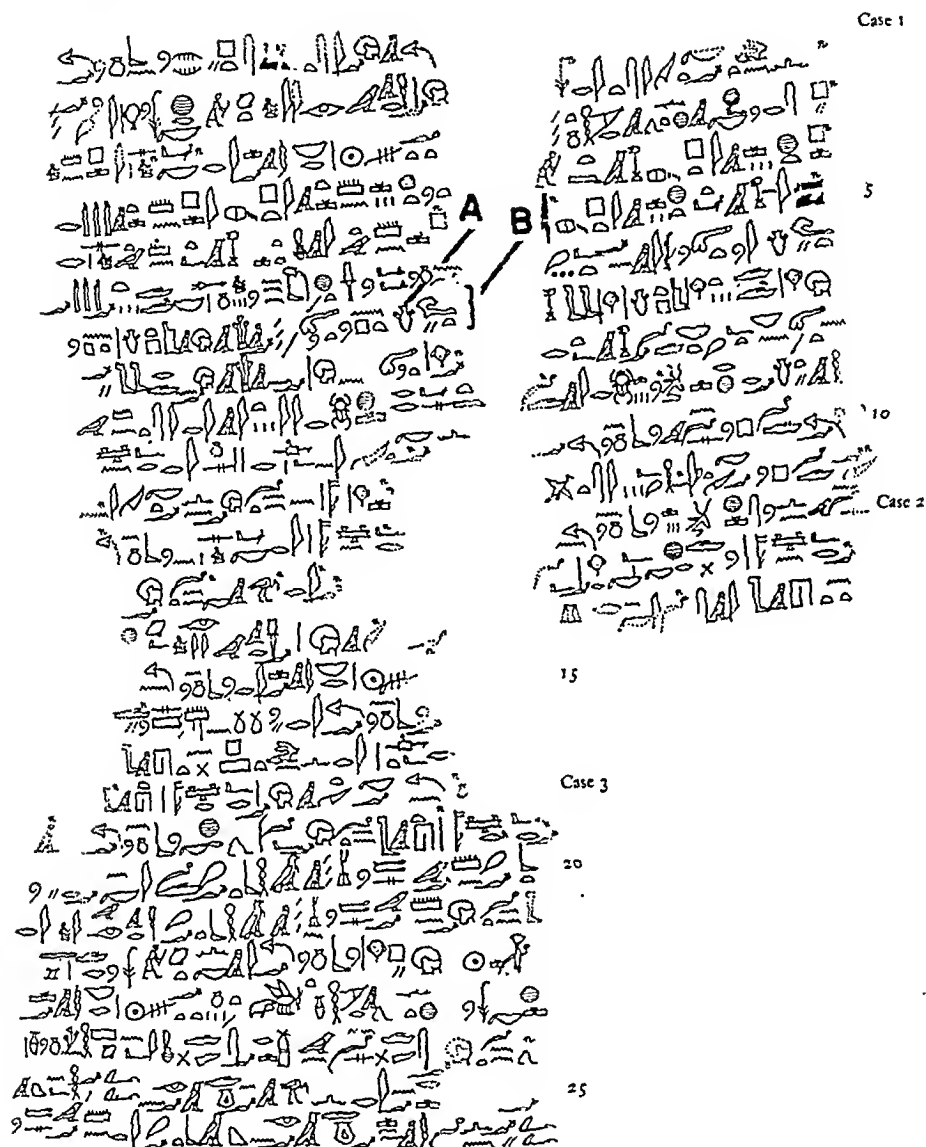


Fig. 2.—Photograph of the facsimile of the hieroglyphic transliteration of Column I (cases of head wounds) of the Edwin Smith Surgical Papyrus. A, Sense sign (ideogram) for the word "heart"; B, sound signs (phonograms) for the word "heart" (hieroglyphic). The ideogram following the phonogram (reading from right to left) is spoken of as the "determinative," as it appears to determine the meaning of the foregoing sound. University of Chicago Press, Chicago, 1930.

Fig. 2 shows a photograph of the facsimile of the transliteration of Column I by a modern scholar from hieratic into hieroglyphic.

The first references to the heart and circulation (pulse) and methods of their examination are found in Case 1 of Column I, which Dr. Breasted translates as follows:

"Now if the priests of Sekhmet or any physician put his hands (or) his fingers [upon the head, upon the back of the] head, upon the two hands, upon the pulse, upon the two feet [he] measures (*h'y*) [to]

the heart, because its vessels are in the back of the head and in the pulse; and because its [pulsation is in] every vessel of every member.'*"

The words enclosed in brackets [] represent those supplied by the translator, because of the "broken and fragmentary" condition of this portion of the column, and therefore cannot be accepted as absolutely conclusive. However, because of the context of the remaining clear portion of the treatise, and because of a parallel in another document (the Papyrus Ebers), there is little doubt of the correctness of this interpretation. One reads and appreciates this ancient methodical and objective description of the pulse, its examination and interpretation, with deepest interest, especially when viewed over the wide expanse of some 5,000 years. How little we realize today, instructor and student alike, the historical background of this simple clinical method, when we examine and palpate for the pulsating radial, carotid, brachial, femoral, dorsalis pedis, and posterior tibial arteries! It was Rokitsansky who advised the medical student of his day "to light his torch on the flame of the ancients," categorical advice which is still applicable.

A second reference to the heart appears in Case VII, Column III, line 3, of the treatise:

"his heart (= 'his spirit' or 'his mind') is too weary to speak, or 'for speech.' His heart beats feebly."

Figs. 3 and 4, photographs of the facsimiles of the hieratic script and the hieroglyphic transliteration of Column III, respectively, contain the material whence this excerpt is taken. As is evident, "our

*Dr. John A. Wilson, Director of the Oriental Institute, careful student of the Smith Papyrus, on reviewing this paper, comments on this passage of the papyrus as follows:

"The passage means much the same thing under my translation. As my own translation differs slightly from that of Dr. Breasted, I give it here. If my translation is of any use to you, you are of course welcome to it.

'[As for] those (members on) which (A) the priests of Sekhmet or any physician puts his hands (or) his fingers: [upon the head, upon the back of the] head, upon the two hands, upon the location of the heart (B), (or) upon the two legs [he] measures (h'y) [for] (C) the heart. That is to say (D), its vessels are in the back of the head and in the location of the heart; that is, [it speaks throughout] every vessel of every member.'

A. For syntax, cf. K. Sethe, *Erläuterungen zu den altägyptischen Lesestücken* (Leipzig, 1927), 58, 15 to 17.

B. Literally 'place of the heart'; probably the physical location of the organ. So H. Grapow, *Ueber die anatomischen Kenntnisse der altägyptischen Aertzen* (Leipzig, 1935) p. 15. Note that a "favorite" is "he of the place of the heart"—Erman & Grapow, *Wörterbuch*, IV, 4.

C. 'Measure to' would probably be h'y r. Here we have, from the Ebers parallel, h'y n, 'measure for.'

D. The Ebers parallel has hr ntt 'because of the fact that.' But here we have nt pw, which Gardiner, *Egyptian Grammar*, No. 190,2, gives as 'that is.'

In connection with this passage, one is struck by the close parallel found in the Ebers papyrus: (The Papyrus Ebers; Translated by B. Ebbell.) pp. 114 to 115.

"XCIX. There are vessels from it to every limb. As for this, when any physician, any surgeon (lit. Saehmet-priest) or any exorcist applies the hands or his fingers to the head, to the back of the head, to the hands, to the place of the stomach, to the arms or to the feet, then he examines the heart, because all his limbs possess its vessels, that is: it (the heart) speaks out of the vessels of every limb."

The close similarity of these two passages suggests that the original writer of these two papyri (Ebers-Smith) was one and the same, or that they were two individuals, one copying from the other, or that, finally, the passage in both papyri was copied from a much earlier source, antedating both,

ancient surgeon" amplifies the simple observation of the heart to include the concept of a failing or feeble organ, perhaps thus demonstrating his astuteness of observation and clinical experience. The phrase "too weary to speak!", suggestive of the tired heart, expresses the skill and artistry of the ancients.

The Egyptian word for heart, a conventionalized picture of the organ, may be found in the hieratic script of Column I, line 7 (Fig. 1); it is the character identified with the black arrow. Through the kindness of Dr. John A. Wilson, director of the Oriental Institute, University of Chicago, I was enabled to secure a pictorial enlargement of the word (Fig. 5). Likewise, the hieroglyphic analogue for heart, indicated with the arrow in Fig. 2, has been enlarged for easier identification in Fig. 6. Thus we have graphic evidence of the introduction into ancient Egyptian writing of the word "heart." To some extent we may visualize the gross appearance of the heart from the hieroglyphic heart sign, particularly, as we shall see (p. 269), because it symbolizes the ox heart, and identifies the base and apex of the heart and the bilateral symmetrical projections, the pulmonary artery and aorta, respectively.

In connection with the above, we may consider here certain data concerned with these early Egyptian records: "The hieroglyphic form of inscription was employed chiefly on monuments, consisting of birds, beasts, men or definite objects, sculptured in stone or painted on wood. The hieratic writing, on the other hand, was used in the sacred and medical papyri. The emblems used in the hieroglyphics are contracted, mere indications being used to save the trouble of forming complete pictures of birds, beasts, etc. Thus, when copying or passing from stone to papyrus, it became essential to use some form of cursive writing for ease in execution, whence the development of hieratic script."⁶

The hieroglyphic sign for the heart may be found in A. H. Gardiner's Egyptian grammar,⁷ the authoritative textbook of ancient Egyptian now used by all English-speaking Egyptologists. In Fig. 7, a photostat of page 456 of the grammar, one sees the heart sign No. 34 marked with arrow. In further explanation and elucidation of ancient Egyptian, Gardiner writes as follows: "Even in the fully developed form of hieroglyphic writing only two classes of signs need be clearly distinguished. There are, first, *sense* signs or *ideograms*, and second, *sound* signs or *phonograms*. Ideograms, or sense signs, signify either the actual object depicted . . . or else some closely connected notion. Ideograms or sense signs . . . are signs that convey their meaning pictorially. . . . In several of the examples quoted . . . the ideogram follows

one or more phonograms and ends the word. In such cases as these it is called a *determinative*, because it appears to determine the meaning of the foregoing sound." In the definition of the heart sign (Fig. 7, No. 34) one may then identify the sign used first as an ideogram, and that in the latter part of the definition as a determinative to clarify the preceding written phonograms. One may now turn back to Fig. 2, where on close inspection it may be seen that the heart sign is also used as a determinative following the phonograms, reading from right to left, the usual direction of ancient Egyptian writing.



Fig. 3.—Photograph of the facsimile of Column III of the Edwin Smith Surgical Papyrus. University of Chicago Press, Chicago, 1930.

Further usage of the heart sign is found in the German dictionary of Erman and Grapow, "Wörterbuch der aegyptischen Sprache," Vol. I^s (Figs. 8 and 9). Beginning with the heading "das Herz," page 59, a wide variety of expressions in which the word heart is included is listed, and the list is continued on page 60. Many of these phrases were taken from the widely known and carefully studied and translated Papyrus Ebers (George Ebers—1875⁹).

And finally, it may be of interest to quote the following from Warren R. Dawson.¹⁰ "It is a noteworthy fact that the various hieroglyphic signs representing parts of the body and especially the internal organs are pictures of the organs of mammals and not of human beings. This shows that the Egyptian knowledge of the internal structure of animals is older than their knowledge of that of man.

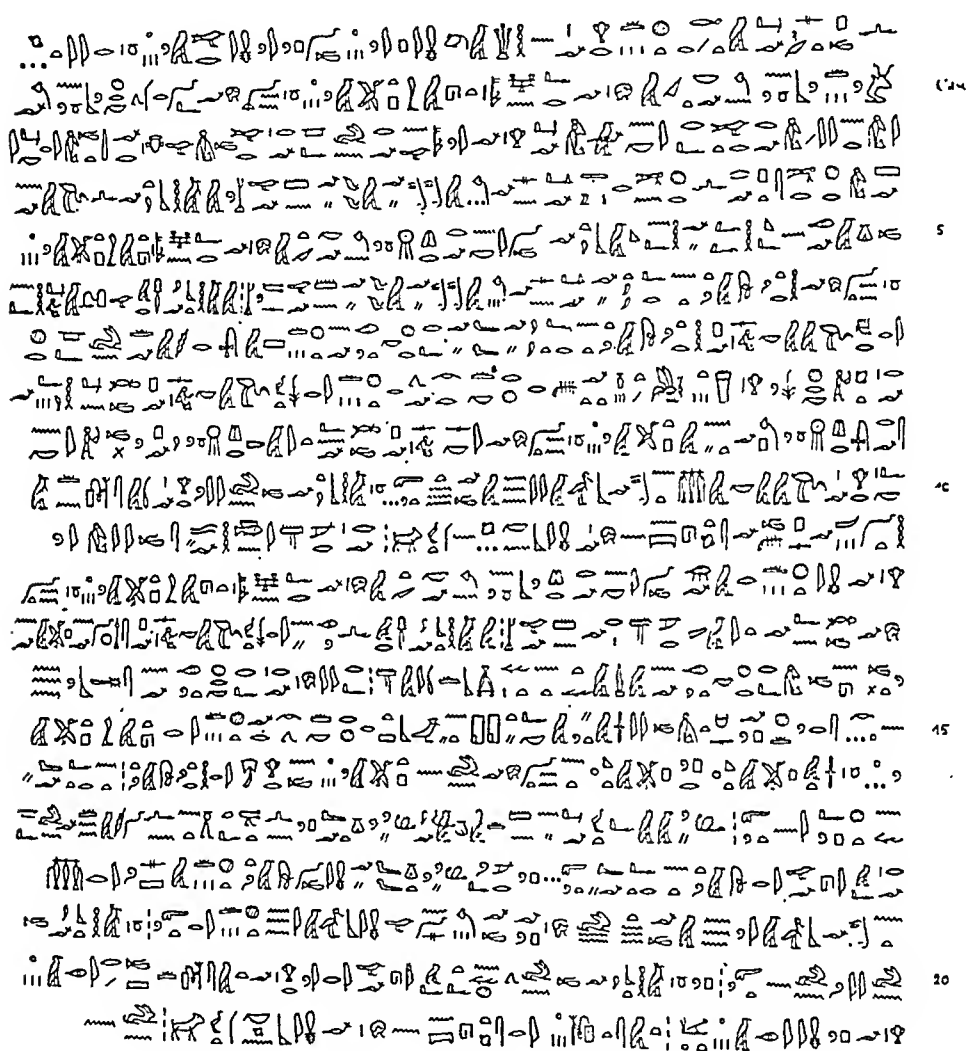


Fig. 4.—Photograph of the facsimile of the hieroglyphic transliteration of Column III, dealing with head wounds, from the Edwin Smith Surgical Papyrus. University of Chicago Press, Chicago, 1930.

It shows, further, that they recognized the essential identity of the two, for they borrowed the signs based on the organs of animals and used them unaltered when speaking of the corresponding organs of the body. Thus the hieroglyphic for heart is the heart of an ox and not that of a man."

This brief consideration of the earliest known reference to the heart and circulation, contained in the Edwin Smith Surgical Papyrus, may



Fig. 5.—Enlarged photograph of the Egyptian word for "heart," taken from line 7, Column I, of the Edwin Smith Surgical Papyrus. University of Chicago Press, Chicago, 1930.

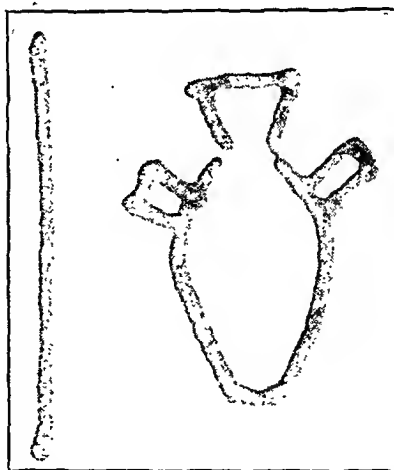


Fig. 6.—Enlarged photograph of the hieroglyphic analogue of the Egyptian word for "heart," taken from line 7, Column I, of the Edwin Smith Surgical Papyrus. University of Chicago Press, Chicago, 1930.

Sign-list

EGYPTIAN GRAMMAR


































- F 29  hide of leopard (?) pierced by an arrow Ido. or det. in  var.  *stl* (*stl*)¹ 'pierce' and derivatives. Also phon. *st*, ex.  *stt* 'the goddess' Satis². in spite of the fact that Pyr. write this name  *stt* with *t* instead of *f*.
¹ *Dyn.* 1192. ² *Proc. Mus.* 1911. ³ *Dyn.* 1116; see *Id.* 41, 11
- 30  water-skin Cf.  *stt* 'water-skin',¹ 'cushion'.² Hence phon. *st*, exx.  var. Pyr.  *stt* 'draw forth';  var.  *stt* 'address', 'question'.
¹ *Proc.* 11, 119; cf. *Proc.* 11, 119; *Id.* 41, 11. ² *Proc.* 11, 119; *Id.* 41, 11. ³ *Dyn.* 1035. ⁴ *Proc. Mus.* 1911, 3.
- 31  three foxes' skins tied together Cf.  *stt* 'apron of foxes' skins'. Hence phon. *st* (*st*). exx.  *stt*, var. Pyr.  *stt*, 'give birth';  *stt* 'black eye-paint'.
¹ *Id.* 41, 11. ² *Proc.* 11, 119. ³ *Dyn.* 1035. ⁴ *Id.* 41, 11.
- 32  animal's belly showing teats and tail Ido. in  *stt* 'belly', 'body'. Hence phon. *st*.
¹ *Id.* 41, 11. ² *Proc.* 11, 119. ³ *Id.* 41, 11.
- 33  tail Det. in  *stt* (*stt*)¹ 'tail'. Hence phon. or phon. det. *st*, ex.  var.  *stt*, a title B C
¹ *Id.* 41, 11. ² *Proc.* 11, 119. ³ *Id.* 41, 11. ⁴ *Id.* 41, 11.
- 34  heart Ido. in  var. Pyr.  *stt* 'heart'. Det. in  *stt* 'heart'.
¹ *Dyn.* 1011.
- 35  heart and windpipe¹ For unknown reason, phon. *st* in  *stt* 'good' and related words.
¹ *Id.* 41, 11. ² *Proc.* 11, 119. ³ *Id.* 41, 11. ⁴ *Id.* 41, 11.
- 36  lung and windpipe¹ Cf.  *stt* 'lung'. Hence phon. or phon. det. *st* (*st*) in  var.  *stt* (*stt*)² 'unite' and derivatives.
¹ *Id.* 41, 11. ² *Id.* 41, 11. ³ *Id.* 41, 11. ⁴ *Dyn.* 1011.
- 37  backbone and ribs Ido. or det. in  var.  *stt* 'back'. Det. in  *stt* 'back'. By confusion with  M 21, phon. det. *st* in  *stt* 'succour'.
¹ *Id.* 41, 11. ² *Id.* 41, 11. ³ *Id.* 41, 11. ⁴ *Proc. Mus.* 1911; *Id.* 41, 11; *Id.* 41, 11.
- 38  alternative to last (Dyn. XVIII) Det. in  *stt* 'back'.
¹ *Id.* 41, 11. ² *Id.* 41, 11. ³ *Id.* 41, 11.
- 39  backbone with marrow issuing from it¹ Ido. in  var.  *stt* 'marrow', whence also  var.  *stt* 'venerated state'. Rarely det. in  *stt* 'back'.
¹ *Id.* 41, 11. ² *Id.* 41, 11. ³ *Id.* 41, 11. ⁴ *Dyn.* XVIII, *Id.* 41, 11.

Fig. 7.—Photostat of page 456 of A. H. Gardner's "Egyptian Grammar," showing the Egyptian word for "heart," No. 34 of the sign list. A, Ideogram; B, phonogram; C, determinative. Clarendon Press, Oxford, 1927.

perhaps be of interest to medical men and students of medical history in emphasizing once again how very distant and far reaching are the roots of our knowledge in the biological sciences. It is surely with a deep sense of reverence that we of the present day are privileged to look back through these long vistas of growing human wisdom and understanding, may catch the first glimmerings of conscious scientific enquiry and observation, can appreciate the "flame of the ancients," lighting the torch of knowledge in the domain of the heart and circulation, and can see it carried forward so brilliantly by "our ancient

a) „zwischen“ zwei oder mehr Dingen 1.

r iwd r „zwischen“ und 2.
r iwd ... r iwd „zwischen“ und zwischen ... 3.

b) bei „jem. 4. bei“ etw 5.
 etw. liegt jemandem ob 6.

iwd.t Trennung ? 7. Sit. M.R.

iwd im Netz fangen 8. D. 20
 vgl. i3d.t „Netz“.

iwdn8 ein Bräucherwerk 9. Sit. M.R.

i8 das Herz.
 semit. l3, l3.

A. als Körperteil des Menschen 10 und auch der Tiere 11.
 vgl. h3tj.

B. bildlich = Mittelpunkt, Centrum 12, insbesondere in hr - i8 (vgl. bei hr).

C. bildlich 13 als Sitz des Denkens, Fühlens, Wollens u.s.w.
 Die meisten Ausdrücke dieses häufigsten Gebrauchs des Wortes siehe bei den anderen Bestandteilen.

Im Einzelnen sonst:

I. Verstand, Gedanke 14.
 (vgl. auch imj.t - i8 u.s.w.).

i8 n n8w.t „Verstand des Königs“ als Bez. eines Beamten u.ä. 15.

i8 n r „Verstand des Re“ als Beiname des Phioth 16 und auch des Chons 17. Gr.

II. Gewissen 18, Charakter 19.

III. Stimmung 20.

Fig. 8.—Photostat of page 59 of Erman and Grapow's "Wörterbuch der aegyptischen Sprache" Vol. I, showing various usages of the Egyptian word for heart, beginning with "das Herz." J. C. Hinrichs'sche Buchhandlung, Leipzig, 1926.

surgeon" (Imhotep ?), Aristotle, Praxagoras, Herophilus, Galen, Vesalius, Colombo, Harvey, Malpighi, Thebesius, and their many contemporaries, pupils, and descendants.

It is a pleasure to express to Dr. John A. Wilson, Director of the Oriental Institute, University of Chicago, my deep sense of indebtedness for his kindness and assistance in the preparation of this paper. I am likewise greatly indebted to Dr.

IV. Verschiedene Ausdrücke:
































<u>n</u> <u>ib</u> <u>f</u>	nach seinem (o.ä.) Wunsch (<u>tu</u> u.ä. w.) 1.	
<u>nj</u> <u>ib</u>	Liebling u.ä. 2	 , 
<u>nj</u> <u>s.t</u> <u>ib</u>	Liebling u.ä. 3.	
<u>n</u> <u>ib</u> <u>n</u>	aus Liebe zu 4; wegen 5; damit 6.	 
<u>ntt</u> <u>m</u> <u>ib</u>	was man wünscht 7. u.ä.	 
(<u>n</u>) <u>dn</u> <u>ib</u>	sowie man will (u.ä.) 8.	 
<u>rdj</u> <u>ib</u>	unter Anderem:	
<u>rdj</u> <u>ib</u> <u>n</u>	das Herz zuwenden zu: 9.	 
<u>rdj</u> <u>ib</u> <u>m</u> <u>h3</u>	sich kümmern um... 10.	  
<u>rdj</u> <u>ib</u>	Ausdruck für „gehen“, „kommen“ 11. <u>Er.</u>	 
<u>ib</u>	wie ein Verbum gebraucht: <u>Seh</u> <u>Lit</u> <u>MR.</u>	
<u>ib</u> <u>f</u> <u>n</u>	sein Herz steht nach..., er wünscht 12.	 
<u>ib</u> <u>tw</u> <u>n</u>	man wünscht zu tun 13.	 
<u>ib</u>	ein Pflanzenteil in: <u>ib</u> <u>n</u> <u>dn</u> <u>ag</u> 14. <u>Nä.</u>	  
<u>ib</u>	feindlich gegen (n)? 15. <u>Sp.</u>	
<u>ib</u> (?)	Bez. des Apophis 16. <u>Sp.</u>	
<u>ib</u>	Art Baum: sein Laub zu kränzen 17. sein Holz zu einer Statue 18. <u>Per.</u> ; <u>Sn</u> <u>N.R.</u>	   

Fig. 9.—Photostat of page 60 showing a variety of phrases in which the Egyptian word for heart is portrayed in Vol. I of the "Wörterbuch der ägyptischen Sprache," Erman and Grapow. J. C. Hinrichs'sche Buchhandlung, Leipzig, 1926.

Louis N. Katz, Director of Cardiovascular Research, Michael Reese Hospital, for many helpful criticisms. I am likewise indebted to the Oriental Institute for permission to reproduce various photographs of facsimiles from the "Edwin Smith Surgical Papyrus" (Figs. 1 to 6 inclusive); to the Clarendon Press for permission to reproduce photostat of page 456 of A. H. Gardiner's "Egyptian Grammar" (Fig. 7); and to J. C. Hinrichs'sche Buchhandlung for permission to reproduce photostats of pages 59 and 60 of Erman and Grapow's "Wörterbuch der ägyptischen Sprache" (Figs. 8 and 9).

REFERENCES

1. Cannon, Walter B.: The Value and Harm of Scientific Controversy, An address delivered at the annual meeting of Alpha Omega Alpha, Atlantic City, 1937.
2. Stern, Bernhard J.: Social Factors in Medical Progress, New York, 1927, Columbia University Press.
3. Breasted, James Henry: The Oriental Institute, p. 410, Chicago, 1933, University of Chicago Press.
4. Haddad, Sami I., and Khairallah, Amin A.: A Forgotten Chapter in the History of the Circulation of the Blood, *Ann. Surg.* 104: 1, 1936.
5. Breasted, James Henry: The Edwin Smith Surgical Papyrus: Published in Facsimile and Hieroglyphic Transliteration With Translation and Commentary in Two Volumes, Vol. I, Foreword p. XVIII, Chicago, 1930, University of Chicago Press.
6. Finlayson, James: Ancient Egyptian Medicine: A Bibliographical Demonstration in the Library of the Faculty of Physicians and Surgeons of Glasgow, Jan. 12, 1893; *Brit. M. J.*, May 13-20, 1893.
7. Gardiner, A. H.: Egyptian Grammar, Oxford, 1927, Clarendon Press.
8. Erman, Adolf, and Grapow, Hermann: Wörterbuch der ägyptischen Sprache, Vol. I. J. C. Hinrichs'sche Buchhandlung, Leipzig, 1926.
9. Ebers, George: Papyrus Ebers: Das Hermetische Buch über die Arzneimittel der alten Ägypter in Hieratische Schrift (1875), Leipzig, 1913, Walter Wreszinsky.
10. Dawson, Warren R.: Magician and Leech—A Study in the Beginnings of Medicine With Special Reference to Ancient Egypt, London, 1929, Methuen and Co., Ltd.

THE PROGNOSIS OF BUNDLE BRANCH BLOCK*

LOUIS FARGÈRES BISHOP, JR., M.D., AND GEORGE A. CARDEN, JR., M.D.
NEW YORK, N. Y.

SINCE the advent of the electrocardiogram there has been a growing interest in the clinical significance of intraventricular conduction defects of the bundle branch block type. This interest has been fed by a progressive increase in the number of recorded examples. King¹ reports that in 1930 it was found more frequently in the medical wards of Johns Hopkins Hospital than rheumatic or typhoid fever. As King suggests, this is probably due to a freer use of the electrocardiograph rather than to any significant increase in the incidence of the disorder. With few exceptions, the numerous reports of large series of well-studied cases which have appeared in the literature in the past 16 years indicate that the presence of a bundle branch defect, either partial or complete, is presumptive evidence of advanced heart disease and makes the prognosis grave. This is so contrary to our personal experience with a group of 50 patients whom we have followed for periods as long as 20 years that it stimulated the present communication. In this we have attempted to analyze a group of significant reports which have appeared in the literature in the past 16 years, selecting those which lend themselves to a fairly uniform type of analysis, and to compare these with the present small series, in order, if possible, to disclose the factors which influence this discrepancy in prognosis.

REVIEW OF 1,178 CASES FROM THE LITERATURE

Type of Electrocardiogram.—It became apparent to White and Viko,² in 1923, who studied complete and partial bundle branch block separately, that there is little or no difference in the prognosis in the two groups. This observation has been adequately confirmed by Graybiel and Sprague.³ From 395 cases analyzed separately according to type and degree of bundle branch block, they concluded that partial bundle branch block should be regarded clinically as equally as significant as complete bundle branch block, and that the prognosis in both is essentially the same.

The present review of 1,178 reported cases includes only those in which there was a pronounced degree of conduction defect, but no attempt has been made to review them separately with regard to the particular type of conduction defect present.

*Read at the Fourteenth Scientific Sessions of the American Heart Association, June 10, 1938, San Francisco, Calif.

Received for publication July 20, 1938.

Age, Sex, Type of Heart Disease, Associated A-V Block, Cardiac Reserve, and Cardiac Enlargement.—There is a close similarity in most of the statistical data. The age was not averaged in all the reports, but in 60 to 80 per cent of the cases it ranges between 50 and 70 years. In the hypertensive and arteriosclerotic group the average age is higher than in the syphilitic and rheumatic group. In King's¹ series of 150 cases the average age was 61 years, 4 months, in the senile group; 48 years, 3 months, in the syphilitic group; and 42 years, 2 months, in the rheumatic group.

Males invariably predominate, 3 or 4 to 1.

Those patients etiologically classified as having hypertensive or arteriosclerotic heart disease comprise 70 to 80 per cent of the cases, and of these about 50 per cent had had anginal symptoms. The remaining 20 to 30 per cent includes cases of syphilitic and rheumatic heart disease, an occasional case of congenital heart disease, and a few which could not be etiologically classified. The relative incidence of rheumatic and syphilitic heart disease depends upon the geographical distribution of the cases; the incidence of the former is higher in the northeastern United States, and that of the latter is higher in the Southern States.

Associated A-V heart block, partial or complete, was found in various percentages from 3 to 34 per cent. In the 395 cases of Graybiel and Sprague,³ the largest single series reported, A-V heart block, partial or complete, was present in 37 cases, or 9 per cent of the entire series.

The reports did not lend themselves to a statistical analysis of the precise cardiac status of these patients. In Herrick and Smith's⁴ 35 cases all of the patients had "cardiac weakness," and 65 per cent had congestive failure. White and Viko² found congestive failure present in 23, or 56 per cent, of 41 cases reported. Willius⁵ found dyspnea on exertion to be a prominent symptom in all of his 105 cases, in 14 per cent of which frank congestive failure was present. Hill⁶ found pronounced cardiac insufficiency in all of his 41 cases. Campbell and Turkington,⁷ in their series of 56 patients, separated the hospital ward patients from the private ambulatory patients and found a marked degree of myocardial insufficiency in 60 per cent, mostly in the hospital group. Graybiel and Sprague³ observed congestive failure in 118 of their 395 cases. Although King,¹ in the report of his series of 155 hospital cases, does not mention the cardiac status, he does point out that the very fact that the patients were in a hospital indicates that cardiac symptoms were present. In sharp contrast to the observations of others, Wood and his associates⁸ report no evidence of heart disease, aside from the electrocardiographic evidence of a bundle conduction defect, in 31 per cent, no marked heart disease in 23 per cent, and definite heart disease with, and without, failure in 45 per cent of their series of 64 patients.

In the other reports no estimate of the relative cardiac reserve is recorded, but, judging from the 851 cases in which data are available,

it is apparent that, with the exception of the series of Wood, et al.,⁸ cardiac insufficiency was present in a very high percentage of the cases of bundle branch block. In accord with this is the fact that cardiac enlargement (although its presence or absence was not always mentioned) was even more common than frank cardiac insufficiency. For example, in Graybiel and Sprague's³ 395 cases heart size was noted in 166 and found to be larger than normal in 154 of these. Here again the findings of Wood and his associates⁸ do not fall in line with those of others, as they found a very small percentage of patients with cardiac enlargement, and, as would be expected, that these are mainly patients manifesting other evidences of heart disease.

Prognosis.—Of the 1,178 cases reviewed there are follow-up studies reported in 890; these are summarized in Table I. It is immediately evident from this table that the observations of Wood and his associates⁸ differ strikingly from all the others in regard to prognosis. By dividing them into three groups, according to the presence and the degree of heart disease, they show that the prognosis is dependent on the degree of attendant heart disease rather than on the presence of bundle branch block. As all their cases were examples of right bundle branch block, they raise the question whether the location of the bundle branch lesion accounts for the optimistic prognosis or whether their findings apply to bundle branch block of all types. In support of the former possibility they cite 14 cases of right bundle branch block (5 reported by Von Deesten and Dolganos and 9 by Oppenheimer, Rothschild, and Mann), in 12 of which the patients were followed for many years and did not manifest any cardiac symptoms. In support of the other hypothesis, namely, that lesions of the right bundle branch have no special individual prognostic significance, are the following notable observations: (1) Bayley⁹ analyzed 75 cases of right and 103 of left bundle branch block and in referring to both groups collectively says: "The average person with bundle branch block shows little evidence of cardiovascular disease on routine physical examination." As Bayley published no follow-up studies his series is not included in Fig. 1. (2) Campbell and Turkington's⁷ follow-up studies of 56 patients with left bundle branch block,^{*} which showed that the prognosis was good in the non-hospitalized group, further tend to nullify the conception that the optimistic prognosis is limited to patients with defects in the right bundle only. (3) Finally, as mentioned previously, Graybiel and Sprague³ showed quite definitely in a study of a large enough series to carry conviction that neither the type nor the degree of bundle branch block had any special influence on the prognosis. The mere presence of any sort of intraventricular conduction defect, they felt, was of grave prognostic significance.

*Reported as right bundle branch block (old terminology).

TABLE I
PROGNOSIS IN 890 CASES OF BUNDLE BRANCH BLOCK COLLECTED FROM THE LITERATURE

AUTHORS	PATIENTS FOLLOWED	DEAD			LIVING			CASES IN WHICH THE BBB WAS OF UNUSUAL DURATION
		NO.	PER CENT	AVERAGE DURATION OF LIFE AFTER BBB DISCOVERED	NO.	PER CENT	AVERAGE DURATION OF LIFE AFTER BBB DISCOVERED	
Herrick and Smith ⁴	21	11	52	1 yr. 6 mo.	10	48	Not mentioned	None recorded
White and Viko ²	36	26	72	9 mo.	10	28	Not mentioned	None recorded
Hart ¹⁴	21	18	86	9 mo.	3	14	2 yr.	
Willius ⁵	66	43	65	1 yr. 2 mo.	23	27		
Bach ¹⁰	35 (Senile) 13 (Syphilitic) 14 (R.H.)	10 9 1	28 70 13	3 mo. 1 mo. 2 yr.	25 4 7	72 30 87	Not mentioned	2 (senile) living 9-14 yr.
Hille ⁶	15	9	60	1 yr. 2 mo.	6	40	1 yr. 6 mo.	
Campbell and Turkington ⁷	26 (Hosp.) 26 (Nonhosp.)	19 11	70 42	2 yr. 1 yr. 6 mo.	7 15	30 58	5 within 1 yr. 17 for 4 yr. 5 mo.	1 living 7 yr. 1 living 13 yr. 4 living 9 yr.
Graybiel and Sprague ³	308	223	72	1 yr. 2 mo.	85	28	2 yr. 11 mo.	None recorded
King ¹	77 (Senile) 13 (Syphilitic) 14 (R.H.)	54 12 10	70 92 70	1 yr. 10 mo. 2 mo.	23 1 4	30 8 30	1 yr. 9 mo. 1 mo. 2 yr. 8 mo.	*1 for 6 yr. 6 mo. *1 for 2 yr. 1 mo. *1 for 6 yr. 7 mo.
Salcedo-Salgar and White ¹¹	157	96	61	1 yr. 6 mo.	61	39	2 yr. 5 mo.	<i>Living</i> 4 for 4-5 yr. 7 in 4-6 yr. 3 for 8-9 yr. 2 in 8-9 yr. 1 for 11 yr. 1 in 11 yr.
Wood, et al. ⁸	19 (No H.D.) 13 (Slight H.D.) 22 (H.D.)	1 1 6	5 5 30	2 yr. 3 yr. (2 for 2 yr., 4 within 1 yr.)	18	95	3 yr. 6 mo. 3 yr. 8 mo. 2 yr. 10 mo.	19 living 4-6 yr. 2 living 7 yr. 1 living 11 yr.
Totals	890	560	63	1 yr.	330	37	2 yr. 10 mo.	

*Not stated whether living or dead.

The balance of evidence would seem to indicate, then, that the favorable prognosis observed by Wood and his associates⁵ in patients without pronounced evidence of heart disease, other than the electrocardiographic indications of an intraventricular conduction defect, has nothing to do with the fact that they all happened to have right bundle branch block, but is rather to be ascribed to the relatively slight degree of attendant heart disease present.

The high percentage of cardiac insufficiency and cardiac enlargement which occurred in the other groups accounts for the relatively poor prognosis in those groups. With the exception of the nonhospitalized patients of Campbell and Turkington's⁷ series and the selected group reported by Wood and his associates,⁵ roughly 60 to 70 per cent of all the other patients were dead within an average of one year after the discovery of the bundle conduction defect. The survival period of those still living averages 2 years, 10 months. Bach,¹⁰ and also King,¹ both of whom presented their cases separately according to etiology, were in agreement that the prognosis is universally bad in the syphilitic cases, despite the fact that they occur in younger persons, and relatively good in the rheumatic cases. The results of follow-up studies over periods of 4 years or more are not mentioned in all the reports, but the studies which have been made, with the exception of that of Wood, et al.,⁵ which showed that 22 patients, or 40 per cent, were alive 5 years (average) after the discovery of the electrocardiographic abnormality, reveal that few patients survive very long. Two patients, or 3 per cent, of Bach's¹⁰ series were alive after 9 and 14 years, respectively. Campbell and Turkington⁷ report that 6 patients, or 11 per cent, were living between 7 and 13 years after the discovery of the lesion. King¹ mentions only 2 patients, both followed for 6.5 years, but does not state whether they were living or dead at the end of this time. Of 18 of Salcedo-Salgar and White's¹¹ patients (11 per cent of their series) 8 were living and 10 were dead after 6.4 years (average).

PRESENT SERIES

The present series consists of 50 patients seen in private practice during the course of the past 20 years, all of whom were ambulatory when first seen. All of those who are living have been contacted recently, and in cases in which death has occurred, the exact time and, in most instances, the mode of death have been ascertained.

Type of Electrocardiogram.—Only electrocardiograms showing a marked degree of intraventricular conduction disturbance, with QRS intervals of 0.12 second or more, were chosen. Thirty-five were examples of complete left bundle branch block, 5 of complete right bundle branch block, and 10 of intermediate types, differing only from complete bundle branch block in that the T-waves were not in the opposite direction from the main ventricular complex in both Leads I and III.

Age, Sex, Type of Heart Disease, Associated A-V Block, Cardiac Reserve, and Cardiac Enlargement.—As shown in Fig. 1, the average age of the 50 patients when first seen was 59.2 years. The average age of those still living is 10 years less than of those who have died.

Twenty-six per cent, or approximately one-fourth, were women.

When classified etiologically, 43 patients, or 86 per cent, had hypertensive or arteriosclerotic heart disease, 2 had syphilitic aortitis with aortic insufficiency, 2 had rheumatic valvular disease, and 3 were unclassified because they presented no clinical evidence of heart disease other than the electrocardiographic evidence of a bundle conduction defect.

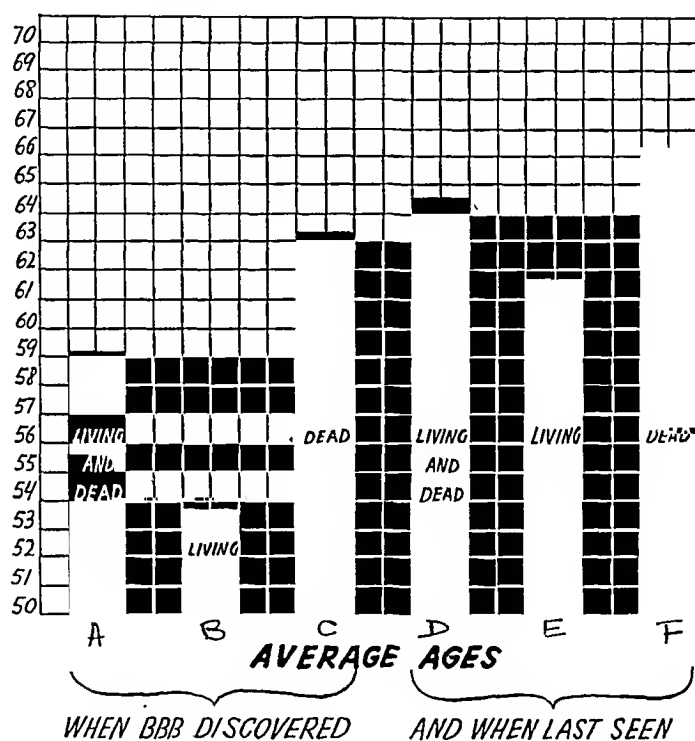


Fig. 1.—Graph showing the total average age of the entire series when first seen, A. The patients are subdivided into those who are still living, B, and those who have died, C, and their ages are compared with similar data when last seen (D, E, F). The age differences between these two groups give the average duration of life for the entire series in those living and those who have died.

Partial auriculoventricular block not due to digitalis administration was encountered only once.

The cardiac reserve at the time of the discovery of the bundle branch block was arbitrarily divided into three classifications: "good," "fair," and "poor." The last was used for patients who had symptoms of cardiac insufficiency while at rest in bed or on very slight exertion. The first was used to signify a response to physical activity not incompatible with the patient's age, though a few patients with mild angina on moderately severe exertion were included in this group. The term "fair"

was applied to those whose cardiac reserve appeared to be between "good" and "poor." Thus classified, the cardiac reserve was found to be "good" in 17 cases, "fair" in 22, and "poor" in 11. With the single exception of one patient who was living 8 years after the first visit, all of the patients with poor cardiac reserve died within 3 years.

Cardiac enlargement, as determined fluoroscopically and teleroentgenographically, was absent in 10 cases, and present in varying degrees in others. Among those patients classified as having a "good" cardiac reserve, the heart was not enlarged in 7, slightly enlarged in 8, and moderately enlarged in 2 (both rheumatic cases). Of those with "poor" cardiac reserve, 2 had slight, 4 moderate, and 5 had marked cardiac enlargement.

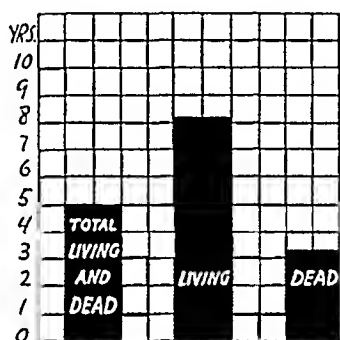


Fig. 2.—Average duration from discovery of bundle branch block until last seen.

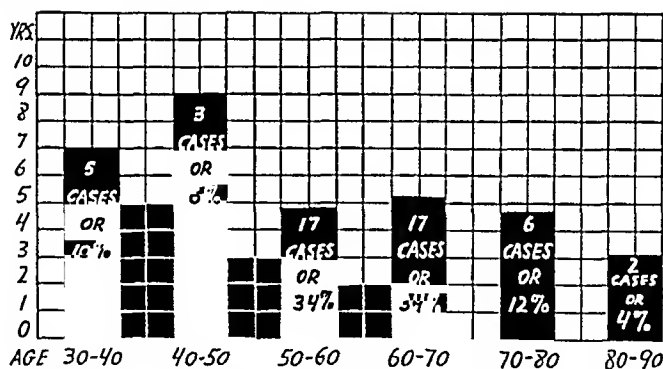


Fig. 3.—Average duration in different age groups from discovery of bundle branch block until last seen.

Prognosis.—As is shown in Fig. 2, the average period of survival from the time of discovery of the bundle conduction defect until last seen is 5 years, 3.2 years for those who have died and 8.2 years for those still living. In Fig. 3 the ages are divided into decades, and the number of cases and average survival periods recorded in each. This shows that the average duration of life is longer among the younger patients. The fact that it happens to be greater in those between 40 and 50 than in those between 30 and 40 is probably not significant in view of the small

number of cases in these groups. Twenty-one patients, or 42 per cent, in our series are living; twenty-nine, or 58 per cent, are dead. The highest mortality occurred in the first 4 years after the discovery of the lesion. Thirty per cent of the deaths occurred in the first year, 15 per cent in the second, 10 per cent in the third, and 8 per cent in the fourth, making a total of 63 per cent within the first four years. In the remaining patients who survived this four-year period the relative mortality decreased progressively, and with each year of survival the total life expectancy increased. Generalizing from these data then, the life expectancy of any patient with bundle branch block, other factors being equal, increases progressively with each year of survival.

Unusual Cases.—Three cases of transient, recurrent, complete bundle branch block are included in our series. In a case previously reported,¹² a man of 64 years with arteriosclerotic heart disease was found to have transient bundle branch block 7 years ago. The transient recurrent nature of the lesion was observed for 3 years. For the past 4 years the block has apparently remained permanent. He continues well and active, without cardiac symptoms.

Another patient, a man of 60 years with anginal symptoms, who had a normal electrocardiogram in November, 1935, was found to have bundle branch block in August, 1936. Three months later he had a small coronary occlusion, but the bundle branch block was not observed again, although numerous electrocardiograms were taken, until January, 1937. It was observed again in March, 1937, and has been present on 4 subsequent occasions. He still has slight angina on exertion, but has had no progression of symptoms since the discovery of the bundle branch block.

The third case of transient bundle branch block occurred in a 58-year-old man with chronic rheumatic heart disease and paroxysmal auricular fibrillation who had had electrocardiograms frequently since 1934; his right bundle branch block was first discovered in January and February, 1936. In January, 1937, he had coronary occlusion, but the bundle branch block did not reappear until January, 1938; since then it has been present in all electrocardiograms, taken at monthly intervals. He has cardiac cirrhosis, persistent recurrent ascites, and edema, and his condition has been growing progressively worse. Despite this, he still manages to get to his office several days a week.

Five patients, two men and three women, who have been followed an unusually long time, are included in the present series; all of them are still living. One is a man now 80 years old, whose bundle branch block was first discovered 17 years ago, at the age of 63, when he came to the office complaining of palpitation and nervousness. Though he has not been seen recently, he is reported to be well and reasonably active for his age.

Another is a woman who was 61 when her bundle branch block was first discovered 18 years ago. At that time she had paroxysmal auricular fibrillation, which became chronic 12 years later. She also developed mild diabetes and osteoarthritis. In a letter from her local doctor enclosing a recent electrocardiogram, he states that she has no cardiac symptoms, but is considerably incapacitated from a combination of old age, diabetes, and arthritis.

The third case¹³ was that of a woman whose bundle branch block was discovered 18 years ago at the age of 47. She has had slight dyspnea on exertion which has progressed very little during the past 18 years. She was seen two months ago. She continues to be active without any significant increase in cardiac symptoms.

The fourth case occurred in a young man with chronic inactive rheumatic heart disease and mitral stenosis whose bundle branch block was first discovered at the age of 26, 19.5 years ago. He is still active and reasonably well, despite fairly marked cardiac enlargement.

The fifth case, in which the duration was longest of all, was that of a woman whose bundle branch block was first disclosed at the age of 52, 20 years ago. Her chief complaint at that time was of a sharp pain in her chest and back more suggestive of neuritic than of cardiac origin. The finding of bundle branch block was quite unexpected. She was then lost sight of, but has been located recently and found to be well and active, without cardiac symptoms at the age of 72.

DISCUSSION

In comparing the present series with the 890 cases collected from the literature in which the patients were followed, it is apparent that there is a significant difference in prognosis between the two groups. This is illustrated in Tables II and III. In Table II the average survival period in these 890 cases is compared with the corresponding data in the present series. The figure of 8 years 2 months for the average duration of life in our living patients is somewhat distorted by the 5 cases in which the bundle branch block was of unusual duration, mentioned above. When these are omitted, the average is 5 years 1 month, still almost twice that in the 890 previously reported cases. Table III compares the individual survival periods in our cases and in those of three of the most optimistic reports in the literature (Campbell and Turkington,⁷ Salcedo-Salgar and White,¹¹ and Wood and his associates⁸). The longest follow-up study previously reported is that of the patient reported to be living and well 14 years after the discovery of the bundle branch block.

In Salcedo-Salgar and White's¹¹ series of 157 cases, 21 patients survived 4 years or more, as compared with 23 for the same period in the present series of 50 cases.

TABLE II

PRESENT SERIES COMPARED TO CASES FROM THE LITERATURE WITH RELATIONSHIP TO
PER CENT OF PATIENTS LIVING AND DEAD AND SURVIVAL PERIODS
IN THESE TWO GROUPS

	TOTAL NUMBER OF PATIENTS FOLLOWED	DEAD			LIVING		
		NO.	PER CENT	AVERAGE DURATION OF LIFE AFTER BBB DISCOVERED	NO.	PER CENT	AVERAGE DURATION OF LIFE AFTER BBB DISCOVERED
Cases from the literature	890	560	63	1 yr.	330	37	2 yr. 10 mo.
Present series	50	29	58	3 yr. 2 mo.	21	42	8 yr. 2 mo.

TABLE III

COMPARISON OF SURVIVAL PERIODS IN OUR CASES (INCLUDING PATIENTS BOTH LIVING
AND DEAD) WITH THOSE IN THE CASES OF THREE OF THE MOST OPTIMISTIC
REPORTS IN THE LITERATURE

SALCEDO-SALGAR, WHITE			CAMPBELL- TURKINGTON		WOOD, ET AL.		BISHOP, JR. CARDEN	
YR.	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Less than 1 year	68	43	22	44	10	18	3	6
1	29	18	11	22	4	7	12	24
2	18	11	4	8	9	17	8	16
3	19	12	5	10	9	17	4	8
4	2	1			9	17	5	10
5	10	6	2	4	9	17	1	2
6	3	2			1	2	3	6
7			1	2	2	4	1	2
8	4	3					2	4
9	2	1	4	8			1	2
10							2	4
11	2	1			1	2	1	2
12							2	4
13			1	2				
14								
15								
16								
17							1	2
18							2	4
19							1	2
20							1	2
Total	157		50		54		50	

CONCLUSIONS

Bundle branch block, partial or complete, is not in itself indicative of severe heart disease, nor of a poor prognosis. The character and degree of attendant heart disease are the principal factor in determining prognosis, and not the presence or absence of bundle branch block.

REFERENCES

1. King, John T.: Bundle-Branch Block: A Case Analysis With Especial Reference to Incidence and Prognosis, *Am. J. M. Sc.* 187: 149, 1934.
2. White, Paul D., and Viko, Louis E.: Clinical Observations on Heart Block, *Am. J. M. Sc.* 165: 659, 1923.

3. Graybiel, Ashton, and Sprague, Howard B.: Bundle-Branch Block: An Analysis of 395 Cases, *Am. J. M. Sc.* 185: 395, 1933.
4. Herrick, James B., and Smith, Fred M.: Clinical Observation on Block of the Branches of the Auriculoventricular Bundle, *Am. J. M. Sc.* 164: 469, 1922.
5. Willins, Frederick A.: Clinical Features of Cases Exhibiting Electrocardiograms Conforming to Those of Experimental Complete Bundle-Branch Block, *AM. HEART J.* 1: 576, 1926.
6. Hill, Ian G. W.: Bundle-Branch Block. A Clinical and Histological Study, *Quart. J. Med.* 24: 15, 1930.
7. Campbell, S. B. Boyd, and Turkington, S. I.: Right Bundle-Branch Block. An Analysis of the Clinical Records of Fifty-Six Cases with Typical Electrocardiograms, *Quart. J. Med.* 24: 481, 1931.
8. Wood, Francis Clark, Jeffers, William A., and Wolferth, Charles C.: Follow-Up Study of Sixty-Four Patients with a Right Bundle-Branch Conduction Defect, *AM. HEART J.* 10: 1056, 1935.
9. Bayley, R. H.: The Frequency and Significance of Right Bundle-Branch Block, *Am. J. M. Sc.* 188: 241, 1934.
10. Bach, Francis: On the Clinical Significance of Right Bundle-Branch Block, *Quart. J. Med.* 23: 261, 1930.
11. Salcedo-Salgar, Jorge, and White, Paul D.: The Relationship of Heart Block, Auriculoventricular and Intraventricular, to Clinical Manifestations of Coronary Disease, Angina Pectoris and Coronary Thrombosis, *AM. HEART J.* 10: 1067, 1935.
12. Bishop, L. F., Jr.: Transient, Recurrent, Complete Left Bundle-Branch Block, *AM. HEART J.* 15: 354, 1938.
13. Bishop, L. F., and Bishop, L. F., Jr.: Bundle Branch Block of Unusual Duration, *J. A. M. A.* 98: 398, 1932.
14. Hart, T. Stuart: Block of the Branches of the Bundle of His. Clinical Notes on the Changes Following the Administration of Digitalis: Comments on the Levocardiogram, Dextrocardiogram and Bicardiogram, *Arch. Int. Med.* 35: 115, 1925.

THE ROLE OF THE TREATMENT OF SYPHILIS IN THE PREVENTION OF CARDIOVASCULAR INVOLVEMENT*

WILLIAM PAUL THOMPSON, M.D., LOS ANGELES, CALIF.,
WILFRID J. COMEAU, M.D., AND PAUL D. WHITE, M.D.,
BOSTON, MASS.†

THE importance of the prevention of syphilitic aortitis, together with the present national interest in the subject of syphilis both among laymen and the members of the medical profession, has made it desirable to attempt a statistical evaluation of antisyphilitic therapy in relation to the later development of cardiovascular involvement. It is the general impression in some localities that cardiovascular syphilis is much less common today than it was two or three decades ago. There are two probable reasons for this. The first is that in cases of aortic regurgitation of uncertain etiology, rheumatic rather than syphilitic involvement of the aortic valve is now considered the more likely, whereas formerly the reverse was usually true; this is especially so in communities where rheumatic heart disease is common. The second reason is the wider application of more effective treatment, which has doubtless been the primary factor in reducing the incidence of the late and serious manifestations of syphilis. To our knowledge, however, such statements as the last are based almost entirely on clinical impressions without the factual support of adequate data. The present study of 260 individuals who contracted syphilis fifteen to twenty-five years ago is an early attempt to supply more concrete information on the relationship of the amount of early antisyphilitic therapy to the incidence of cardiovascular involvement.

The limitations of such a study as this are not readily apparent. It would appear, as it did to us originally, that modern methods of antisyphilitic therapy have been in use long enough to establish their value in the prevention of cardiovascular involvement. Actually, however, adequate antisyphilitic therapy in the light of our present concepts was not practiced until about 1920 and, even then, almost entirely in special clinics or by syphilologists. This is clearly indicated in Tables III and IV, which show that early treatment was far better in those individuals who had their primary syphilis less than twenty years ago than in those infected before that. The reason for this becomes clear when the following facts are considered. Arsenic, the most efficacious of the antisyphilitic drugs, was not introduced by Ehrlich and Hata until 1910, and the development of a clear understanding of its proper use occupied

*From the Cardiac and Luetic Clinics of the Massachusetts General Hospital, and the Luetic Clinic of the Boston Dispensary, Boston.

†With the cooperation of John MacMillan, M.D., Wellford C. Reed, M.D., Samuel Kushman, M.D., N. Bowman Wise, M.D., Francis M. Thurmon, M.D., and Austin W. Cheever, M.D.

Received for publication July 20, 1938.

the greater part of the next decade. Bismuth, which is at present next in importance, did not come into wide usage until after 1925. Furthermore, most of the individuals were treated originally by local physicians whose understanding of the diagnosis and proper treatment of early syphilis was inadequate in most instances. Another difficulty, which the present national campaign should remedy, is the fact that the significance of the early lesions of syphilis is just now being appreciated by laymen. Our experience with the present group showed clearly that most of the individuals were unconcerned by early syphilitic manifestations for which the majority of young people of today would seek medical attention. Because of this it is very difficult to assemble a group, even as small as the present one, of patients with a definite history of early syphilis and anything approaching satisfactory treatment. More years must elapse before it will be possible to follow up the late results (fifteen to twenty-five years after infection) of the *adequate* early treatment of syphilis.

MATERIAL AND METHOD

Selection of Cases.—The cases used for this study were selected from the records of the Massachusetts General Hospital and the Boston Dispensary.* There were two criteria for the selection of each patient: first, a definite history of primary syphilis dating back fifteen to twenty-five years, and second, adequate personal knowledge of early treatment if such information was not already available from hospital records. The presence or absence of a previous diagnosis of cardiovascular syphilis played no part in selection. A minimum of fifteen years was taken because it is known that cardiovascular syphilis becomes manifest in many cases by that time. A maximum of twenty-five years was chosen because antisymphilitic therapy previous to that time was very inadequate as judged by present standards. We have followed up and re-examined 260 individuals in whom the date of the primary syphilis and the early and late specific treatment are known and who form an unselected group with respect to their present clinical condition.

Method of Examination.—In each individual a detailed history of the primary lesion and treatment, together with a cardiovascular history, was taken, and physical and fluoroscopic examinations were carried out. Particular attention was given to the aorta, which was examined with the aid of barium in the esophagus. An orthodiagram was made in each instance. No measurement of the aorta was attempted since there exists no truly reliable method to distinguish between abnormal and normal aortic size unless a gross abnormality is present. Under such conditions aortic dilatation would be readily recognizable without resort to mensuration. Thus the size of the aorta in this study is based entirely on our fluoroscopic impression of its size. Routine electrocardiograms were not taken; they are rarely abnormal except in cases showing easily diagnosable cardiovascular syphilis.

Diagnosis and Grouping of Cases.—Much has been written about the diagnosis of cardiovascular syphilis. Its recognition in the advanced stages is not usually difficult. The criteria for the diagnosis of *early* cardiovascular syphilis, however, vary with different writers on the subject. Perhaps the most generally accepted criteria for the diagnosis of

*Through the courtesy of Francis M. Thimmon, M.D., Chief of the Skin Clinic of the Boston Dispensary, the records of that hospital were made available to us.

uncomplicated aortitis (without aneurysm or aortic regurgitation) are those published by Moore¹ and the Cooperative Clinical Group.² We are convinced, however, that uncomplicated syphilitic aortitis cannot be diagnosed with any degree of certainty unless definite dilatation of the aorta can be shown roentgenologically. A tambour aortic second sound and increased retromanubrial dullness are unreliable signs, in our experience. Furthermore, circulatory embarrassment, progressive cardiac failure, and paroxysmal dyspnea do not occur in syphilitic aortitis except when there is aortic regurgitation or marked narrowing of the coronary orifices; in such instances gross dilatation of the aorta and cardiac enlargement are almost certain to be present. Syphilitic myocarditis as a cause of heart failure is very rare, and angina pectoris in syphilitic heart disease is relatively uncommon. The cardiac functional criteria suggested by Moore and the Cooperative Group are far more likely to be the result of degenerative heart disease in a syphilitic patient than due to uncomplicated syphilitic aortitis.

We³ are convinced that a positive diagnosis of cardiovascular syphilis can be made only when at least one of the following findings is present: (1) a saccular aneurysm of the aorta or innominate artery, (2) aortic regurgitation appearing for the first time in a middle-aged person with a positive serologic reaction for syphilis, or (3) a diffusely dilated aorta without aortic regurgitation or hypertension, past or present. Uncomplicated syphilitic aortitis can be detected only by means of roentgenologic studies, and we agree with the conservative roentgenologic attitude of Steel.⁴ Those experienced in the roentgenologic examination of the heart are aware of the difficulty in discerning slight and at times even moderate degrees of aortic dilatation and, particularly, in ascribing it to syphilis when such possible factors as hypertension and arteriosclerosis are present. Consequently we feel that a positive clinical diagnosis of *early* cardiovascular syphilis is practically impossible.

In view of the above considerations we have divided our material into four clinical groups. First, there is a group with normal hearts without dilatation of the aorta. Varying degrees of aortic tortuosity were present in some of the older individuals in this group, but this finding per se is not to be considered as evidence of cardiovascular syphilis. Second, individuals showing questionable aortic dilatation are so classified implying the possibility but improbability of syphilitic involvement. There are two reasons for our hesitancy about this group: (1) the difficulty in actually determining slight increases in aortic size roentgenologically, and (2) the fact that slight dilatation of the aorta is not uncommon in individuals of this age, particularly when arteriosclerosis is present. Third, individuals with moderate aortic dilatation are classified as having probable aortitis; we do not think sufficient dilatation is present in these cases to be absolutely diagnostic of syphilitic aortitis. And fourth, there is a group with a diagnosis of definite cardiovascular syphilis, made on the basis of the criteria stated above.

Criteria of Treatment.—In view of the diversity of the type, duration, and continuity of treatment in these cases it was difficult to establish criteria which were satisfactory and at the same time sufficiently simple to be applied to a study of this nature. We classified as early treatment any medication given during the first five years after the initial infection. Late treatment was considered to be all medication between six and fifteen years after infection. Treatment beyond fifteen years was not analyzed because we felt that it would not prevent cardiovascular involvement. In view of the fact that antisyphilitic medication other than arsenic and heavy metals given parenterally is relatively ineffective, we established our criteria entirely on the basis of the dosage of arsenic and heavy metals administered by injection. It was not practical to subdivide the types of heavy metal or arsenical preparations. Table I shows the six grades of treatment which we established and the manner in which they are condensed for simplification of discussion. The figures indicate the total number of injections received during each period of treatment (early and late).

TABLE I
NUMBER AND KIND OF INJECTIONS GIVEN IN EACH GRADE OF TREATMENT

GRADE OF TREATMENT	NUMBER OF INJECTIONS	
	ARSENIC	BISMUTH OR MERCURY
0	0	0
I } Very poor	0 - 6	and 0 - 10
II	7 - 12	and 11 plus
III } Poor	13 - 19	and 15 plus
IV } Fair	20 - 29	and 20 plus
V	30 plus	and 40 plus

ANALYSIS OF DATA

Among the 260 individuals were 19 who had heart disease of other than syphilitic etiology. It was considered advisable to avoid all complicating factors, so these were eliminated from the analysis. Table II shows the present cardiovascular status of the remaining 241 patients, who are subdivided according to the time that has elapsed since the initial infection and according to sex. Except for one negro who proved to have cardiovascular syphilis, all of our group were white. The males predominated by a ratio of 5 to 1, with 200 men and 41 women.

It is of interest that 90 per cent of the individuals escaped without clinically detectable cardiovascular syphilis. Doubtless some of the patients classified as having normal aortas or questionable aortic dilatation have a slight degree of syphilitic aortitis which it was not possible to diagnose. This is particularly likely in the light of the pathologic studies of Langer,⁵ Guldberg,⁶ and Warthin,⁷ which indicate that 55 to 86 per cent of syphilitic individuals have microscopic or gross evidence of cardiovascular involvement, although it may not be of any clinical importance.

TABLE II

DISTRIBUTION OF CASES WITH RESPECT TO PRESENT CARDIOVASCULAR STATUS
AND TO SEX

PRESENT CARDIOVASCULAR STATUS AND TIME ELAPSING SINCE INFECTION	MALES	FEMALES	TOTAL	PERCENT* OF TOTAL
Normal hearts and aortas				
15-19 years, inclusive	75	18	93	
20-25 years	82	15	97	
Total 15-25 years	157	33	190	80%
Questionable aortic dilatation				
15-19 years, inclusive	8	3	11	
20-25 years	11	3	14	
Total 15-25 years	19	6	25	10%
Probable aortitis				
15-19 years, inclusive	3	2	5	
20-25 years	3	0	3	
Total 15-25 years	6	2	8	3%
Definite cardiovascular syphilis				
15-19 years, inclusive	5	0	5	
20-25 years	13	0	13	
Total 15-25 years	18	0	18	7%
Grand totals	200	41	241	100%

*Percentages in this and the following tables are expressed to the nearest whole number.

Our figures are quite similar to those of Bruusgaard⁸ and Turner⁹ with respect to the incidence of cardiovascular involvement. The former found that 10 per cent of 473 untreated syphilitics examined ten to thirty years after the primary infection had cardiovascular syphilis, while Turner's⁹ statistical survey of 6000 syphilitics shows an incidence of 7.2 per cent in white individuals (10.1 per cent when negroes were included). By combining our probable (3 per cent) and definite (7 per cent) cases of aortic syphilis, we find an incidence of 10 per cent. (Among our eighteen patients with definite cardiovascular syphilis there were seven with saccular aneurysms, one of whom had aortic regurgitation, and eleven with diffusely dilated aortas, of whom seven had aortic regurgitation.) It is probably safe to say that no more than 10 per cent of white syphilitics, whether treated or not, will develop clinical evidence of cardiovascular syphilis.

Tables III and IV show the pertinent facts regarding the amount of early treatment received by the 241 patients. Inspection of these tables shows that there was very little difference in the amount of treatment received by the individuals who now have normal aortas, questionable aortic dilatation, and probable aortitis, but the eighteen patients with *definite* cardiovascular syphilis without exception received "very poor" or "poor" treatment during the first five years following their infections. Six of the eight patients designated as cases of probable aortitis had very poor early treatment.

It is of interest that the two patients with probable aortitis who received "fair" early treatment were adequately treated, theoretically, since therapy was begun in the early stages of the disease and continued

TABLE III

DISTRIBUTION OF CASES WITH RESPECT TO GRADE OF EARLY TREATMENT

PRESENT CARDIOVASCULAR STATUS AND TIME ELAPSING SINCE INFECTION	EARLY TREATMENT (TOTAL DURING 0-5 YEARS)						TOTAL
	VERY POOR			POOR	FAIR		
	0	I*	II	III	IV	V	
Normal hearts and aortas							
15-19 years, inclusive	21	12	19	15	6	20	
20-25 years	36	24	20	11	2	4	
Total 15-25 years	57	36	39	26	8	24	190
Questionable aortic dilata- tion							
15-19 years, inclusive	0	4	2	3	1	1	
20-25 years	6	3	2	3	0	0	
Total 15-25 years	6	7	4	6	1	1	25
Probable aortitis							
15-19 years, inclusive	1	2	0	0	0	2	
20-25 years	0	1	2	0	0	0	
Total 15-25 years	1	3	2	0	0	2	8
Definite cardiovascular syphilis							
15-19 years, inclusive	2	2	0	1	0	0	
20-25 years	8	4	1	0	0	0	
Total 15-25 years	10	6	1	1	0	0	18
Grand totals	74	52	46	33	9	27	241

*Roman numerals indicate the grades of treatment received; see Table I.

TABLE IV

 DISTRIBUTION OF CASES WITH RESPECT TO GRADE OF EARLY TREATMENT
 (Grades of Treatment Shown in Table III Are Combined Into Very Poor,
 Poor, and Fair)

PRESENT CARDIOVASCULAR STATUS AND TIME ELAPSING SINCE INFECTION	EARLY TREATMENT (TOTAL, DURING 0-5 YEARS)		
	VERY POOR 0, I AND II	POOR III	FAIR IV AND V
Normal hearts and aortas			
15-19 years, inclusive	52 (56%)	15 (16%)	26 (28%)
20-25 years	80 (83%)	11 (11%)	6 (6%)
Total 15-25 years	132 (69%)	26 (14%)	32 (17%)
Questionable aortic dilatation			
15-19 years, inclusive	6 (55%)	3 (27%)	2 (18%)
20-25 years	11 (79%)	3 (21%)	0
Total 15-25 years	17 (67%)	6 (24%)	2 (9%)
Probable aortitis			
15-19 years, inclusive	3 (60%)	0	2 (40%)
20-25 years	3 (100%)	0	0
Total 15-25 years	6 (75%)	0	2 (25%)
Definite cardiovascular syphilis			
15-19 years, inclusive	4 (80%)	1 (20%)	0
20-25 years	13 (100%)	0	0
Total 15-25 years	17 (94%)	1 (6%)	0
Grand totals	172 (71%)	33 (14%)	36 (15%)

for the first two years after the initial infection. The treatment in these two cases is inconsistent with the uniformly "very poor" and "poor" treatment received by all other patients in the series who now have probable or definite aortitis. Because these two patients had aortic dilatation without definite aneurysm or aortic regurgitation, and because the treatment received is at variance with that in the other cases of probable or definite syphilitic aortitis, we may not be entirely justified in regarding their findings as indicative of probable aortitis. The inconsistency in these two cases offers further support of our conservative attitude in adhering to strict criteria for the clinical diagnosis of cardiovascular syphilis.

Of the entire group, 178 individuals received "very poor" late treatment (six to fifteen years after infection), while sixty-three subjects availed themselves of more adequate therapy. Table V shows that "fair" late therapy was given to most of these sixty-three individuals but that only one in each of the groups of patients who now have probable and definite cardiovascular syphilis received late treatment approaching an adequate amount. In both of these cases treatment was not started until ten years after the initial infection; its value in preventing cardiovascular involvement is therefore questionable.

TABLE V
DISTRIBUTION OF CASES WITH RESPECT TO GRADE OF LATE TREATMENT*

PRESENT CARDIOVASCULAR STATUS AND GRADE OF EARLY TREATMENT	TOTAL NUMBER OF CASES	GRADE OF LATE TREATMENT		
		VERY POOR O, I AND II	POOR III	FAIR IV AND V
Normal hearts and aortas				
Very poor	132	94	1	37
Poor	26	21	3	2
Fair	32	20	0	12
Total	190	135	4	51
Questionable aortic dilatation				
Very poor	17	12	1	4
Poor	6	5	1	0
Fair	2	2	0	0
Total	25	19	2	4
Probable aortitis				
Very poor	6	5	0	1
Poor	0	0	0	0
Fair	2	2	0	0
Total	8	7	0	1
Definite cardiovascular syphilis				
Very poor	17	16	0	1
Poor	1	1	0	0
Fair	0	0	0	0
Total	18	17	0	1
Grand totals	241	178	6	57

*Late treatment is herein defined as treatment given after the first five years and through the fifteenth year following the initial infection.

With so few cases of syphilitic aortitis as there are in our series and the generally poor treatment received by nearly all individuals it is difficult to evaluate with certainty the effect of treatment in preventing

aortitis. We must content ourselves with the observation that all of our patients with definite aortitis and three-fourths of those with probable aortitis had inadequate treatment during the first five years after infection, and that only one patient with definite aortitis and one with probable aortitis had treatment of any consequence during the following decade.

SUMMARY

The data on 260 individuals who contracted syphilis fifteen to twenty-five years before this study was made were analyzed in detail with respect to the present cardiovascular status of the subjects and the relationship of treatment thereto. Of these, 19 individuals had heart disease of other than syphilitic etiology and were eliminated from the analysis. Of the remaining 241 patients, 18 (7 per cent) had definite cardiovascular syphilis and 8 (3 per cent) had probable aortitis. In 190 subjects (80 per cent) the heart and aorta were normal, while 25 (10 per cent) had questionable dilatation of the aorta. Our results agree with those of certain other observers in regard to the incidence of cardiovascular syphilis, for we found an incidence of 10 per cent (3 per cent probable aortitis and 7 per cent definite cardiovascular syphilis). The grade of treatment showed little difference in the clinical groups except for individuals with definite cardiovascular syphilis. All of these had inadequate early treatment and in all but one instance the late treatment was no better. There was only one negro in our entire group.

The data accumulated in this study, although necessarily unsatisfactory in certain respects, give some support to our clinical impression that adequate treatment of syphilis tends to prevent the later clinical manifestations of cardiovascular syphilis. Our material should be useful as a basis for comparison in future studies which should be made when time and education have eliminated many of the present difficulties in attempting such an analysis.

We wish to express our gratitude to Miss Marguerite Flood, of the Social Service Department of the Massachusetts General Hospital, for her cooperation and invaluable help in this study.

REFERENCES

1. Moore, J. E.: *The Modern Treatment of Syphilis*. Page 280, Springfield, Ill., 1933, Charles Thomas, Publisher.
2. Cole, H. N., Usilton, L. J., Moore, J. E., O'Leary, P. A., Stokes, J. H., Wile, U. J., Parran, T., and Vonderlehr, R. A.: *Cardiovascular Syphilis. Cooperative Clinical Studies in the Treatment of Syphilis*. Ven. Dis. Inform. Vol. 17, No. 4, April, 1936.
3. White, P. D., and Wise, N. B.: *The Early Diagnosis of Cardiovascular Syphilis*. New England J. Med. 217: 988, 1937.
4. Steel, D.: *The Roentgenological Diagnosis of Syphilitic Aortitis: A Review of Forty Proved Cases*, AM. HEART J. 6: 59, 1930.
5. Langer, E.: *Die Häufigkeit der luetischen Organveränderungen, insbesondere der Aortitis luetica*, München. med. Wchnschr. 73: 1782, 1926.
6. Guldberg, G.: *Über Sektionsbefunde bei Syphilitikern*, Arch. f. Dermat. u. Syph. 166: 730, 1932.
7. Warthin, A. S.: *The Lesions of Latent Syphilis*, Southern M. J. 24: 273, 1931.
8. Bruusgaard: Quoted by Moore, page 278.
9. Turner, T. B.: *The Race and Sex Distribution of the Lesions of Syphilis in 10,000 Cases*. Bull. Johns Hopkins Hosp. 46: 159, 1930.

THE EFFECT OF CERTAIN PURE DIGITALIS-LIKE GLUCOSIDES ON THE FROG'S HEART

A. GARRARD MACLEOD, M.D.
NEW YORK, N. Y.

IN 1915, Cohn, Fraser, and Jamieson¹ described the characteristic effects of digitalis on the T-wave of the human electrocardiogram, and recommended the observation of these effects as a means of following the action of the drug in patients. The method has been applied extensively ever since in clinical medicine. It is surprising, therefore, that similar methods have been so little used in animals. Since the studies of such investigators as Straub,² practically no attention has been paid to changes in the form of the electrogram or electrocardiogram of animals under the influence of the drugs of the digitalis group. Lewis and his collaborators³ and Love⁴ used electrical records in investigating their effect on the refractory period of the heart, but did not study alterations in the form of the curves.

Since the researches of Dr. W. A. Jacobs and his collaborators^{5, 5a} into the chemical constitution of certain digitalis-like glucosides have made available quantities of these substances in pure crystalline form, it seemed worth while to investigate their effect on cardiac action currents. Furthermore, the work of Craib,⁶ Wilson, Macleod, and Barker⁷ and Macleod⁸ has made it possible to interpret electrograms rationally. A study of the effect of these pure glucosides on the frog's electrogram should give, therefore, an insight into their effect on certain of the fundamental properties of heart muscle, and consequently make it possible to understand more clearly the significance of the changes which they and similar substances produce in the human electrocardiogram.

METHOD

All of the experiments were performed on the Louisiana bull frog (*Rana catesbiana*). The animals were pithed, care being taken to avoid loss of blood. The heart was exposed by removing the sternum and slitting the pericardium, but left in situ. Electrograms were recorded from the surface of the heart by the unipolar method described by Wilson, Macleod, and Barker.⁷ The exploring electrode (the one in contact with the heart) consisted of a thread, moistened with saline solution, projecting from the end of a silver tube whose inner surface was coated with silver chloride. The indifferent electrode (the one at a distance from the heart) was a silver plate, 1 cm. by 5 cm., coated with silver chloride, and it was placed beneath the skin of the hind leg. Since the resistance of the exploring electrode was high, a one-stage direct current amplifier was used in conjunction with the string galvanometer.

From the Hospital of the Rockefeller Institute for Medical Research, New York.
Received for publication Aug. 15, 1938.

During the experiment the thread projecting from the end of the silver tube was held in place by surface tension; it was sufficiently limber to follow the movements of the heart. In many experiments a cephalocaudal lead was also taken by placing an electrode in contact with the larynx and pairing it with the indifferent electrode.

When refractory periods were measured, a neon tube stimulator was adjusted to deliver shocks at a rate slightly slower than the existing heart rate. The stimuli were delivered to the tissue by means of a platinum electrode, the terminals of which were placed astride the exploring electrode. This method of obtaining the record from the region stimulated was adopted because Drury and Love⁹ have shown that an impulse arising just after the end of the refractory period may be conducted decrementally. A large deflection caused by the stimulus was recorded in the electrogram, but it did not interfere with the interpretation of the record nor endanger the string of the galvanometer.

The drugs were dissolved in alcohol and diluted to the proper strength with Howell's solution. The dose usually used was 0.03 mg. per 100 gm. of frog. This was sufficient to produce profound effects and was often lethal in from one and one-half to three hours. All drugs were given intravenously into the lateral cutaneous vein. The total volume injected in this way never exceeded 1 c.c.

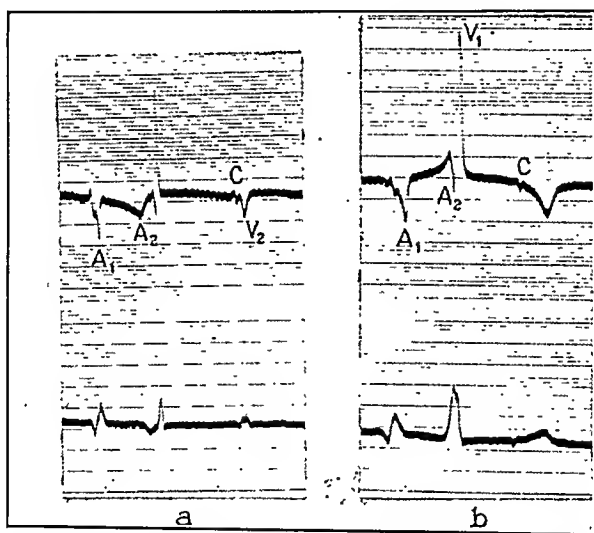


Fig. 1.—The effect of atropine on the frog's electrocardiogram and electrogram. The upper curve in each case is a direct lead from the auriculoventricular junction. The lower curve is an indirect lead from the region of the larynx to the left hind leg. A₁, auricular accession deflection; A₂, auricular regression deflection (T-wave); V₁, ventricular accession deflection (QRS); V₂, ventricular regression deflection (T-wave); C, conal accession deflection. *a* was taken before the injection of atropine sulfate and *b* six minutes after 5 mg. were given into the lateral cutaneous vein.

It has been customary in studying the effect of digitalis bodies to eliminate the influence of these substances on the vagus mechanism by a previous administration of atropine. In most of the experiments here described this procedure was omitted. In the first place, it is generally agreed that in frogs the vagus nerves play no role in the action of these drugs and, secondly, it was found that atropine in doses of 1.0 mg. per 100 gm. of frog produced marked distortion of the electrogram (Fig. 1). This effect upon the complexes (a widening) is neither similar nor in antithesis to the change produced by the glucosides. Smaller doses did not influence the effect of the glucosides, although they abolished completely the effect of large doses of acetylcholine.

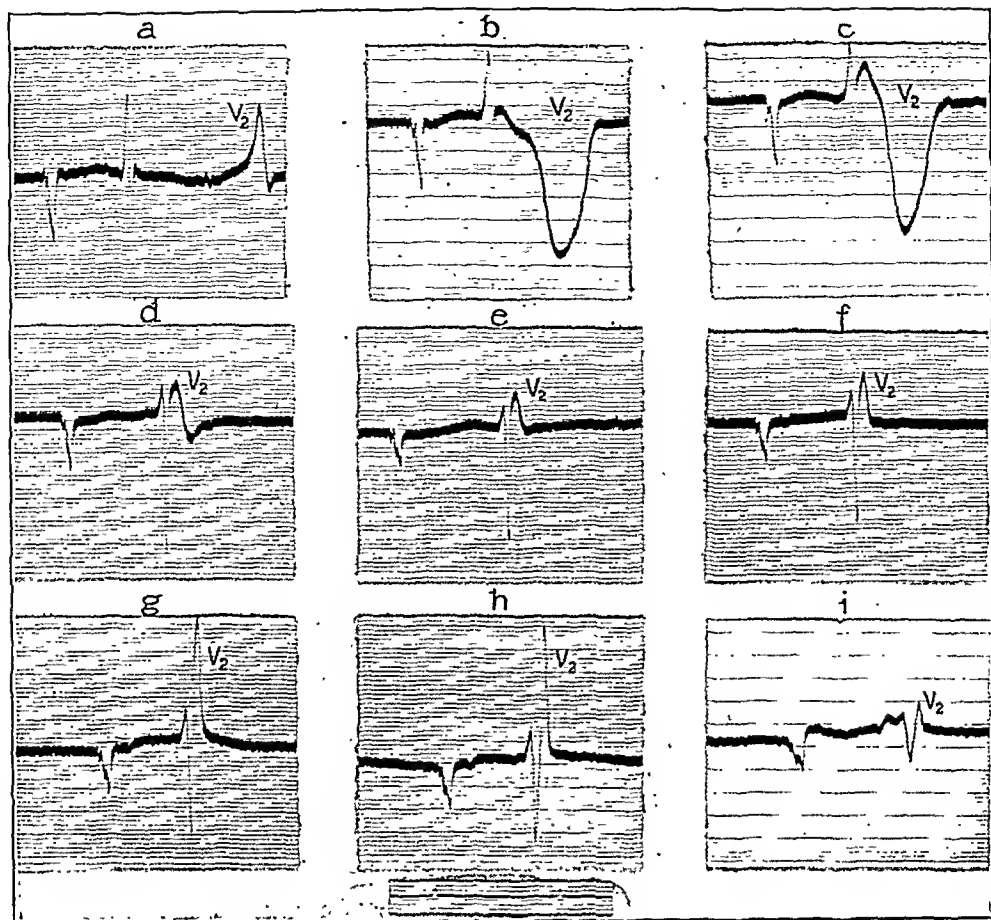


Fig. 2.—The effect of cymarin on the ventricular electrogram. The exploring electrode was on the ventricle, almost at the A-V groove. V_2 is the ventricular regression deflection. *a* was taken before the administration of the drug. *b* was taken 12 minutes after a dose of 0.03 mg. of cymarin per 100 gm. of frog was injected into the lateral cutaneous vein. *c* was taken 20 minutes after the injection. *d* was taken 25 minutes after the first injection and 5 minutes after a second injection. *e*, *f*, *g*, *h*, and *i*, were taken 30, 34, 49, 56 and 66 minutes, respectively, after the first injection.

RESULTS

The first effect of cymarin on the ventricular electrogram (Fig. 2*b*) is inversion and increase in amplitude of the regression deflection (T) and shortening of electrical systole (Q-T). Later (Fig. 2*c*), an upward phase makes its appearance. Still later, the amplitude of the downward phase decreases rapidly until only the upward deflection remains. The duration of the regression process (T) steadily decreases, meanwhile, until (Fig. 2*h*) it is almost as brief as QRS. The primary change brought about by cymarin is, therefore, shortening of the duration of the T deflection, and consequently of electrical systole. As will be shown later, even the great inversion of T (Fig. 2*b*) can be explained as the result of shortening. Slight changes in amplitude occur in the QRS, but its duration is little affected.

To be certain that true shortening of electrical systole occurs under the influence of this drug, an area on the surface of the ventricle was

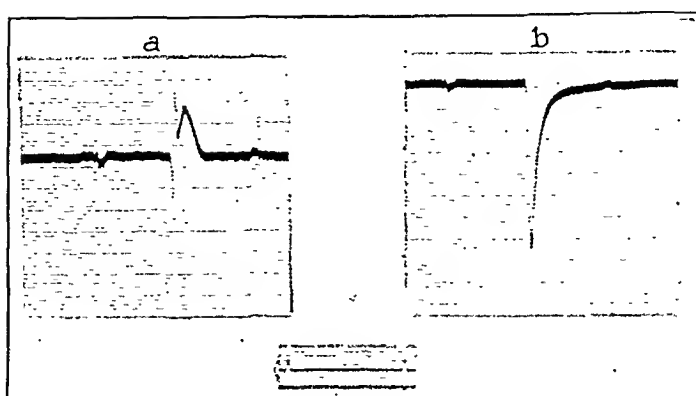


Fig. 3.—The effect of cymarin on the monophasic response. *a* is an electrogram recorded from the central part of the ventricle 80 minutes after the injection of 0.03 mg. of cymarin per 100 gm. of frog. The duration of electrical systole is greatly shortened. *b* is an electrogram taken from the same spot as *a* after burning the area with a hot wire. The curve was taken about 10 minutes after *a*.

burned after an unequivocal effect was produced with cymarin, and a monophasic response recorded (Fig. 3*b*). The duration of electrical systole is essentially the same in the monophasic curve as in the response obtained before injury (Fig. 3*a*). Both are short.

In order to ascertain if a similar effect is produced in auricular muscle, the exploring electrode was placed on the central part of the auricle. Since ventricular systole occurs before the auricular electrogram is complete, heart block was produced by Stannius' ligature. When auriculoventricular dissociation has been established, the ligature

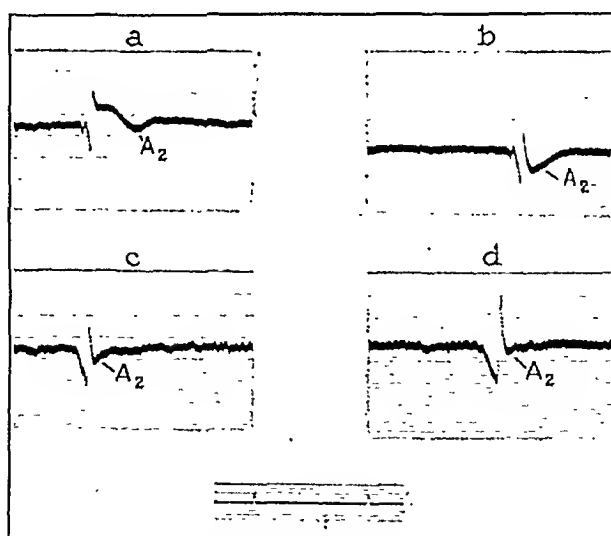


Fig. 4.—The effect of K-strophanthin-beta upon the auricular electrogram. The exploring electrode was at the center of the anterior surface of the auricles. Heart block was produced fifteen minutes after the drug was injected. *A₂* is the auricular regression deflection. *a* is the first curve taken after heart block was produced, about 18 minutes after the injection of the drug. Some shortening of electrical systole has already taken place. *b*, *c*, *d*, were taken 25, 35, and 45 minutes, respectively, after the injection.

may be released so that the force of the auricular contractions and the occasional ventricular beats will cause the circulation to continue even though it is greatly slowed. The effect of the drug in this case is similar, though perhaps less striking, to that produced on the ventricle (Fig. 4). In this case the drug used was K-strophanthin-beta. Cymarin acts similarly. The illustrations have been picked purposely from experiments with different drugs in order to emphasize their close similarity.

TABLE I

		DURATION OF ELECTRICAL SYSTOLE (SECONDS)	DURATION OF REFRACTORY PERIOD (SECONDS)
Normal ventricle		1.15	1.04
Before cymarin		1.01	0.98
After cymarin	1*	0.69	0.48
	2	0.54	
	3	0.37	0.21
	4	0.47	0.34
	5	0.53	0.42
	6	0.34	0.28
	7	0.24	
	8	0.45	0.35
	9	0.41	0.21
	10	0.40	0.22

*Determination 1 was made about fifteen minutes after the administration of cymarin. The interval between the other determinations was about ten minutes.

TABLE II

		DURATION OF ELECTRICAL SYSTOLE (SECONDS)	DURATION OF REFRACTORY PERIOD (SECONDS)
Auricle before cymarin	1	0.77	0.60
	2	0.78	0.61
	3	0.80	0.63
Auricle after cymarin	1	0.24	0.21
	2	0.27	0.23

It has long been thought that there is an association between the T deflection and the end of the refractory period (Mines,¹⁰ De Boer,¹¹ Wilson and Hermann¹²). It seemed important to learn if this relationship persists when hearts are under the influence of these cardiac glucosides. The data in Table I indicate that it does. The first item is the average of a number of measurements of the duration of electrical systole and of the refractory period in a normal ventricle. The remainder of the table gives the results obtained in a single experiment in which the durations of electrical systole and of the refractory period were ascertained from time to time after the administration of cymarin. The shortening of electrical systole by the drug is accompanied by a corresponding shortening of the refractory period (Table I). In this experiment the shortening of the refractory period was much greater than that observed by Love⁴ in the ventricle of a tortoise under the influence

of strophanthin, but the greater effect depends probably on the use of a proportionately larger dose. In the case of both electrical systole and the refractory period, shortening is followed by slight lengthening and, in turn, by shortening. This cyclic variation was very often encountered and frequently continued over quite long periods of time. Similar experiments on the auricle are more difficult to carry out, but the results are similar to those just described for the ventricle (Table II). In general, it may be said that the effect of the strophanthin glucosides on both auricles and ventricles is to shorten electrical systole and the refractory period.

Except for quantitative differences, the effects of the glucosides assayed (cymarin, K-strophanthin-beta, digitoxin, periploeymarin, and ouabain) were indistinguishable from each other.

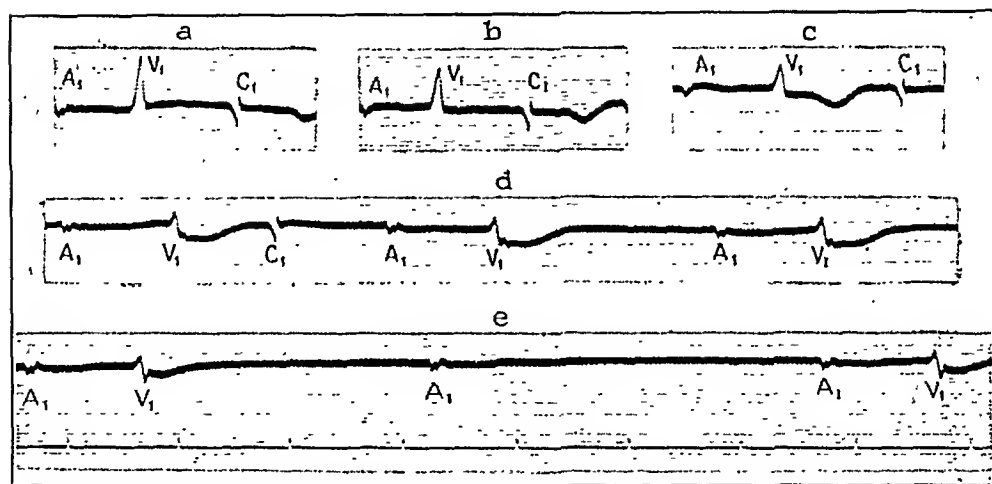


Fig. 5.—The effect of periploeymarin on conduction. The lead is from the larynx to the left hind leg. A_1 , V_1 , C_1 are respectively the auricular, ventricular and conal accession deflections. *a* was taken before the administration of the drug. *b* was taken 2 minutes after 0.03 of periploeymarin per 100 gm. of frog. A-V and V-C intervals are slightly shortened. *c* was taken 10 minutes after injection. A-V and V-C intervals are lengthened. *d* was taken 50 minutes after injection; partial V-C block is present. *e* was taken 73 minutes after injection; both A-V and V-C block are present.

In the later stages of their action, heart block was observed. The development first of ventriculoconal block and later of auriculoventricular block following the administration of periploeymarin is shown in Fig. 5. Sinoauricular block can also be observed late in an experiment after a large dose, but records showing this phenomenon are difficult to obtain because of the small amplitude of the sinus electrogram. Cushny¹³ noted the development of sinoauricular block following the development of auriculoventricular block, but ventriculoconal block seems not to have been reported previously. This orderly development of block, first between conus and ventricle, then between ventricle and auricles, and finally between auricles and sinus, is of interest because

it may be another example of the greater vulnerability of structures which develop later phylogenetically.

Occasionally rhythms suggesting auricular flutter or fibrillation occurred, especially when K-strophanthin-beta was given. These occurred at a time when the refractory period was short. Furthermore, in the process of studying the refractory period, multiple responses were often obtained to single early stimuli when the refractory period had been shortened by the administration of one of the drugs. This phenomenon was not observed in the normal heart.

DISCUSSION

In 1913, Clark and Mines,¹⁴ in a preliminary communication, reported that they had found a reduction in the duration of electrical systole and of the refractory period of the perfused frog's ventricle on the administration of strophanthin (probably on account of Mines' untimely death a fuller account of these observations was not published). Nevertheless, since then little importance has been attached to the duration of electrical systole. Recently, however, studies have appeared which indicate that in certain clinical conditions it is appreciably altered. Prolongation of the interval has been observed by White and Mudd¹⁵ and Barker, Johnston, and Wilson¹⁶ in conditions in which the calcium content of the blood is low. The opposite effect has been noticed by Cheer and Dieuaide,¹⁷ who have demonstrated, by taking careful account of the variations in heart rate, a small but definite decrease in the Q-T interval following the administration of therapeutic doses of digitalis. Their results have recently been confirmed by Larsen, Neukirch, and Nielsen.¹⁸ Observations on the refractory period of cardiac muscle under the influence of drugs are also not very numerous. It was originally held by Lewis and his collaborators that the refractory period of cardiac muscle was prolonged by strophanthin. Their observations were made on dogs whose vagi had been inactivated by atropine. Later, Drury and Love⁹ and Love⁴ showed that in hearts under the influence of veratrine, quinidine, or strophanthin, a stimulus falling just after the end of the absolutely refractory period gives rise to a response which may be conducted decrementally and consequently may not be detectable at a distance from its point of origin. Consequently, refractory periods ascertained by the use of older methods which judged the end of the refractory state by the first response that spread widely, rather than the first produced, may have been too long. Love⁴ found that strophanthin actually shortened the refractory period of the ventricle of the tortoise. Lewis and Drury¹⁹ have admitted the validity of this criticism of their earlier work, but maintain that what they had originally obtained was the "effective refractory period," and that this,

rather than the true refractory period, was germane to their observations on the effect of quinidine and strophanthin on circus movement.

From the data of the experiments reported here it is impossible to ascertain whether conduction with a decrement occurred. A single direct lead was usually taken in the manner described. There was always a slight deformity of the electrograms caused by the stimulus when it fell at any time during the inscription of the curve. When a response was elicited a very definite modification of this artifact occurred, and a wave easily identified as T was apparent. T-waves under these circumstances furnish an unequivocal criterion of a response. Usually, when the heart was under the influence of the drugs an early response was followed, furthermore, by a paroxysm of fibrillation which could not, of course, fail to be detectable even at a distance from the point stimulated. Whether the early responses not accompanied by fibrillation would have been detectable in an indirect lead cannot be stated with certainty, for such a lead was not taken. These responses were large in the direct lead, but deflections in such a lead are, of course, largely produced by muscle very close to the exploring electrode. It is also possible, since early responses are smaller than later ones, that very early responses are so small that they are concealed by the stimulus artifact. While it seems probable that the changes in the refractory period here observed were gross enough to have been detected by any method, the question whether the early responses were conducted decrementally cannot be determined definitely from these experiments.

In a general way, the observations now recorded are in harmony with reports in the existing literature, although a true estimation of the value of these various results in establishing a generally accepted conception is difficult because the experiments have been performed on such a wide variety of subjects, from frogs to man.

Larsen, Nenkirch, and Nielsen¹⁸ refer to the experiments of Wiggers and Stimson,²⁰ in which it was shown that digitalis and strophanthin shorten the isometric contraction and ejection phases when these are ascertained from curves of intraventricular and aortic pressures, as corroborating their own observation that these drugs shorten electrical systole. It is inadvisable to place too much stress upon this point, however, for knowledge of the relationship between mechanical and electrical responses of heart muscle is incomplete. While a close relationship undoubtedly exists between the beginning of the two responses, their ends have not been shown to coincide. It is perhaps more correct to surmise that Wiggers' results, taken in conjunction with the observations that electrical systole shortens under the influence of drugs of the digitalis group, indicate that mechanical and electrical systole under these circumstances vary in the same direction. This is an important relationship and more direct proof of its validity is highly desirable. That mechanical and

electrical systole do not always vary in the same way is indicated by the finding of Barker, Johnston, and Wilson¹⁶ that the marked increase in duration of electrical systole resulting from hypocalcemia is not accompanied by an increase in length of mechanical systole. Of the three entities, mechanical systole, electrical systole, and refractory period, the third appears to be closely linked to the second. The first may also be related to the second, but further evidence is necessary to establish to what extent and under what circumstances this correspondence can be relied upon.

It is the effect of these drugs on mechanical systole that is important to learn in order to decide whether benefit results from their administration apart from slowing the heart rate. The alteration of the refractory period is probably responsible for their well-known tendency to occasion auricular fibrillation and, in toxic doses, ventricular ectopic rhythms. It may also play a role in slowing the ventricular rate in auricular fibrillation. Changes in duration of electrical systole are important principally in so far as they may be used to measure alterations in one or the other of the properties just mentioned (mechanical systole or refractory period). They also may serve as a useful indication that the drug has had an effect.

Further, can the shortening of electrical systole which these drugs produce account for the changes in form (reduction in height or inversion of the T-wave) that have been observed by Cohn, Fraser, and Jamieson¹ and subsequent observers? It is possible that it can. The duration of activity differs, as is already known, in different parts of the heart. If it is shortened, it is not likely to be decreased precisely to the same extent in every region; for instance, it might be shortened most in muscle fibers in which it was initially longest. If this occurred, the order in which various regions pass out of the active state, and consequently the form of the T-wave, would be changed. The following explanation, which accounts for the change in form of the T-wave between Fig. 2*a* and Fig. 2*b*, will make this point clearer.

Before the administration of the drug, Fig. 6*A* may represent schematically the state of affairs. The muscle at the base of the ventricle upon which the electrode rests is the last to pass out of the active state, and the boundary between active and resting muscle is retreating toward *P*. Consequently, *P* is negative, but the boundary eventually passes under *P*, and now, since the positive side of the boundary is nearer *P*, this in turn becomes positive. The state of positivity is brief, for *P* is near the A-V boundary. If, now, a drug is given which shortens the duration of electrical systole and affects the muscle at the base ahead of the muscle elsewhere (possibly because it is thinner), the muscle at the base will pass out of the active state first, and Fig. 6*B* will represent the situation. The boundary will be retreating from *P* and conse-

quently render it positive throughout the period of regression. This explanation is intended to show only that shortening of electrical systole can change the form of the T-wave. Further investigation is necessary before it can be stated that the changes observed in electrocardiograms of patients treated with digitalis actually are produced in this way.

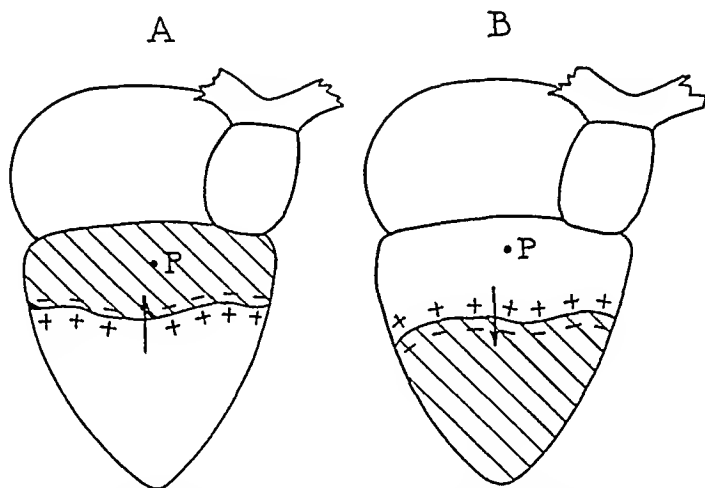


Fig. 6.—Diagram of frog's heart to show change in course of the regression process resulting from local shortening in the duration of electrical systole. *P* is the point on which the electrode rests. The shaded region is the active muscle.

Finally, the close association between the duration of electrical systole and the length of the refractory period confirms the concept of Macleod⁸ that the T-wave is produced by the recovery process. If this is true, the chief effect of these drugs is to hasten recovery. Recovery may not be so complete, however, as in the normal heart, for the QRS deflection is usually reduced in amplitude. This may be caused by a reduction in the potential difference between active and resting muscle, which in turn may indicate a reduction in the difference in their chemical and physical constitution.

SUMMARY

Certain glucosides of the digitalis group have been found to reduce the duration of electrical systole (Q-T) of both the auricles and ventricle of the frog. The refractory period is shortened *pari passu* with this reduction of electrical systole. It was not possible to bring out any differences in the mode of action of the various glucosides tested by the methods used.

REFERENCES

1. Colin, A. E., Fraser, F. R., and Jamieson, R. A.: The Influence of Digitalis on the T-Wave of the Human Electrocardiogram, *J. Exper. Med.* 21: 593, 1915.
2. Straub, H.: Der Einfluss von Strophanthin, Adrenalin und Muskarin auf die Form des Elektrokardiogrammes, *Ztschr. f. Biol.* 53: 106, 1909.
3. Lewis, T., Drury, A. N., and Hieseu, C. C.: Some Observations Upon Atropine and Strophanthin, *Heart* 9: 21, 1921-22.

4. Love, W. S. Jr.: The Effect of Quinidine and Strophanthin Upon the Refractory Period of the Tortoise Ventricle, *Heart* 13: 87, 1926.
5. Jacobs, W. A.: The Chemistry of the Cardiac Glucosides, *Physiol. Rev.* 13: 222, 1933.
- 5a. Elderfield, R. C.: The Chemistry of the Cardiac Glycosides, *Chem. Rev.* 17: 187, 1935.
6. Craib, W. H.: A Study of the Electrical Field Surrounding Active Heart Muscle, *Heart* 14: 71, 1927.
7. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Distribution of the Action Currents Produced by Heart Muscle and Other Excitable Conducting Media, *J. Gen. Physiol.* 16: 423, 1933.
8. Macleod, A. G.: The Electrogram of Cardiac Muscle: An Analysis Which Explains the Regression or T Deflection, *AM. HEART J.* 15: 165, 1938.
9. Drury, A. N., and Love, W. S.: The Supposed Lengthening of the Absolute Refractory Period of the Frog's Ventricular Muscle by Veratrine, *Heart* 13: 77, 1926.
10. Mines, G. R.: On Dynamic Equilibrium in the Heart, *J. Physiol.* 46: 349, 1913.
11. De Boer, S.: The Influence of Veratrin Poisoning on the Electrogram of the Frog's Heart, *J. Physiol.* 49: 310, 1914-15.
12. Wilson, F. N., and Hermann, G. R.: An Experimental Study of Incomplete Bundle Branch Block and of the Refractory Period of the Heart of the Dog, *Heart* 8: 229, 1921.
13. Cushny, A. R.: The Action and Uses in Medicine of Digitalis and Its Allies, p. 50, London, 1925, Longmans Green & Co.
14. Clark, A. J., and Mines, G. R.: The Action of Strophanthin Upon the Excised Frog's Heart, *J. Physiol.* 47: 7, 1913.
15. White, P. D., and Mudd, S. G.: Observations on the Effect of Various Factors on the Duration of Electrical Systole of the Heart as Indicated by the Length of the Q-T Interval of the Electrocardiogram, *J. Clin. Investigation* 7: 387, 1929.
16. Barker, P. S., Johnston, F. D., and Wilson, F. N.: The Duration of Systole in Hypocalcemia, *AM. HEART J.* 14: 82, 1937.
17. Cheer, S. N., and Dieuaide, F. R.: Effect of Digitalis on the Duration of Electrical Systole in the Normal Heart, *Chinese J. Physiol.* 5: 217, 1931; Studies on the Electrical Systole ("Q-T" Interval) of the Heart. IV. The Effect of Digitalis on Its Duration in Cardiac Failure, *J. Clin. Investigation* 11: 1241, 1932.
18. Larsen, K., Neukirch, F., and Nielsen, N. A.: Electrocardiographic Changes in Normal Adults Following Digitalis Administration, *AM. HEART J.* 13: 163, 1937.
19. Lewis, T., and Drury, A. N.: Revised Views of the Refractory Period in Relation to Drugs Reputed to Prolong It and in Relation to Circus Movement, *Heart* 13: 95, 1926.
20. Wiggers, C. J., and Stimson, B.: The Mechanism of Cardiac Stimulation by Digitalis and G-Strophanthin, *J. Pharmacol. & Exper. Therap.* 30: 251, 1927.

THE EFFECT OF ACETYL-BETA-METHYLCHOLINE ON THE FROG'S HEART

A. E. COHN, M.D., AND A. G. MACLEOD, M.D.
NEW YORK, N. Y.

THE vagomimetic character of acetylcholine and closely related compounds has been demonstrated many times on many structures. In the heart the effect of vagus stimulation is quite complex. Gaskell¹ pointed out four aspects of the effect to which Engelmann² has given names: first, a reduction of heart rate (chronotropic); second, a diminution in the strength of contraction (inotropic); third, a decrease in the speed of impulse conduction (dromotropic); fourth, a decrease in excitability to direct stimulation (bathmotropic). To these must be added two other effects, a diminution in the duration of the excited state as evidenced by a reduction in the duration of the electrical response, described by Mines,³ and the production of aberrant auricular rhythms, described by Lewis⁴ and Robinson.⁵

In the study of acetylcholine and its relatives only chronotropic and inotropic effects have received much attention. The dromotropic effect has often been observed but has not proved a useful criterion of the action either of the vagi or of acetylcholine. The bathmotropic effect seems to be confined to the frog's heart and has not been much studied. Reduction in the duration of the electrical response and the production of ectopic rhythms, although highly characteristic of vagus stimulation, have scarcely been studied at all in connection with the action of acetylcholine and its relatives. It is important, however, to know if the choline produce these effects, particularly if the drugs are to be given clinically. Goldenberg and Rothberger⁶ have shown that large doses of acetylcholine produce something akin to auricular fibrillation in mammals. Abnormal rhythms may, therefore, occur in patients. While intense vagus stimulation is required to induce aberrant rhythms, Frederiq⁷ has recently shown that a single shock to the right vagus nerve of the turtle will cause shortening of electrical systole in the auricle for several cardiac cycles. If the choline also produce this change it is possible that the cardiac effect of the drugs can be observed and analyzed electrocardiographically.

METHOD

The experiments to be reported here were all performed on the Louisiana bullfrog (*Rana catesbeiana*) at room temperature. The preparation and method of obtaining electrograms were similar to those described by Macleod⁸ in his study of

From the Hospital of the Rockefeller Institute for Medical Research, New York.
Received for publication Aug. 15, 1938.

the strophanthin glucosides. The heart was exposed and a unipolar direct lead taken from either auricle or ventricle simultaneously with a cephalocaudal lead. The method used for measuring the refractory period has also been described.⁸ The test stimulus was applied to the point from which the direct lead was derived.

The drugs were dissolved in Howell's solution and injected into the lateral cutaneous vein. Acetyl-beta-methylcholine (mecholyl) was used in a concentration of 0.01 mg. per cubic centimeter. As a rule, 0.1 c.c. of this solution was sufficient to bring on a marked effect in a large frog (300 to 400 gm.). The atropine solution used contained 1.0 mg. per cubic centimeter. One-tenth cubic centimeter of this solution would abolish the effect of acetyl-beta-methylcholine in the amounts used for a period of approximately three hours. By itself, this amount of atropine had no effect on the electrogram.

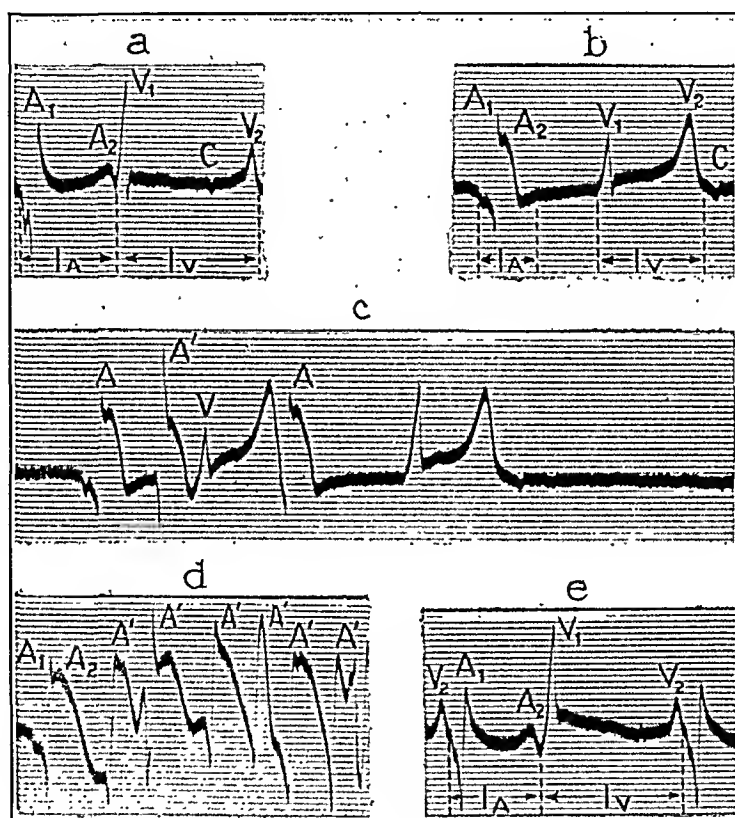


Fig. 1.—Electrograms from frog's auricle. The exploring electrode was near the center of the anterior surface, but closer to the A-V than to the S-A junction.

a is the control before giving the drugs. *A*₁ is the auricular accession deflection. *A*₂ is the final part of the auricular regression deflection. Before it is quite complete, *V*₁, the ventricular accession deflection, occurs. *V*₂ is the final part of ventricular regression deflection. *C* is the conal accession deflection. The conal regression deflection is combined with *V*₂. *1A* is the duration of the electrical response (electrical systole) in the auricle. *1V* is the duration of electrical systole in the ventricle.

b is about one minute after giving 0.1 c.c. of acetyl-beta-methylcholine solution (0.01 mg./c.c.) intravenously.

c shows a spontaneous auricular extrasystole *A'* during height of the drug's action.

d shows spontaneous auricular fibrillation, *A*₁ *A*₂ the last regular auricular complex. *A'* *S* are aberrant complexes.

e shows the return to the original state after administration of 0.01 c.c. of atropine solution (1 c.c. = 10 mg.).

CURVE	1A SEC.	1V SEC.	A-V INTERVAL	A-C INTERVAL
a	0.52	0.72	0.52	0.50
b	0.37	0.58	0.66	0.66
c	0.50	0.75	0.52	0.52

RESULTS

Following the injection of 0.1 c.c. of acetyl-beta-methylcholine solution the effect comes on quickly, often before the needle can be withdrawn. In some cases complete diastolic standstill occurs for a minute or more, in others merely marked bradycardia. With larger doses, periods of asystole of much greater length can be obtained. When an ectopic rhythm develops it usually occurs shortly after the period of most marked slowing. It is as a rule quite transient, but occasionally lasts for a considerable period of time (until the effect of the drug subsides). The maximum effect of the drug usually occurs within two minutes, and it passes off quite completely in about twenty minutes. Sinoauricular block often occurs but auriculoventricular block is seldom seen.

None of the electrograms showed dropped beats, but there was frequently moderate prolongation of the auriculoventricular and ventriculoconal intervals (Fig. 1b). In this respect acetyl-beta-methylcholine does not accurately imitate vagus stimulation, for stimulation strong enough to produce as marked sinus slowing as the drug produces would certainly cause a much higher degree of auriculoventricular block.

The most striking effect of the drug on the electrogram is shortening of the duration of the electrical process in each of the chambers. Some change in shape of the accession* deflection is usually seen, but the deflection is not shortened. The shortening of the electrical response is brought about entirely by the decreased duration of the regression (V_2 or T) deflection.

The course of events in a typical experiment in which the exploring electrode was on the anterior surface of the auricle, near the center but somewhat closer to the auriculoventricular junction than to the sinoauricular, will illustrate these changes (Fig. 1). Auricular (Fig. 1a, A_1 and A_2), ventricular (V_1 and V_2), and conal (C) complexes can be made out. The drug was administered between the time of taking Fig. 1a and Fig. 1b, and the administration was followed immediately by a period of asystole. Because of this period it is impossible to follow the early changes in the regression process, for the drug has meanwhile had time to exert its full effect, so that when spontaneous contraction is resumed the change in form of the curve is already fully developed.

The auricular accession deflection (Fig. 1b, A_1) is somewhat changed in form and may be slightly increased in duration, but since its final

*The frog's electrogram is the composite of the electrograms of each of its four chambers, sinus, auricle, ventricle, and conus, which beat serially. Of these only the sinus produces effects too small to be detected in the records. The electrogram of each chamber consists, furthermore, of two parts, a rapid deflection accompanying the accession of activity (the QRS of the human electrocardiogram) and a slower one accompanying regression of activity (T-wave). In a curve of such complexity the usual electrocardiographic method of naming the parts of the curve is entirely inadequate. In this paper, the terms accession and regression deflection will be used for the rapid and slow deflections, respectively, and will be modified by an adjective denoting their origin. This method of naming the parts of the curve was suggested by Macleod.⁹

portion is combined with the initial part of the regression deflection it cannot be accurately measured. This combination of the two deflections also contributes to the change in shape of the accession deflection. The regression deflection (A_2) is greatly reduced in duration and increased in amplitude. This change is similar to that observed by Macleod¹⁰ under the influence of heat.

In the case of the ventricle the accession deflection is decreased in size but is approximately of the same duration. But the terminal portion of the regression deflection (V_2) moves from a position to the right of the conus deflection (C) to a position between V_1 and C, and increases conspicuously in amplitude.

The conus complex is too small to be analyzed in these curves. Its regression deflection in this case cannot be made out. Under favorable conditions the complete complex can be seen, but the regression deflection is usually combined with the final part of the ventricular regression deflection or with the succeeding auricular complex. The effect of the drug on the conus seems, however, to be similar to its effect on the other chambers.

Auricular extrasystoles develop (Fig. 1c) and short periods of impure flutter or fibrillation (Fig. 1d). All of these phenomena are transient. The curve returns to its original form promptly on the administration of atropine (Fig. 1e).

It is sometimes possible to observe the changes in form of the curves as the effect of the drug progresses. In an experiment in which heart block had been produced by Stannius's ligature so that the *auricular complex* could be seen undistorted, the accession deflection (Fig. 2b, following the administration changed little except to decrease somewhat in size. The regression deflection at first becomes large and diphasic (Fig. 2b). Then, while retaining its diphasic character, it decreases in duration (Fig. 2c, d, e). In returning to its normal form as the effect of the drug wears off the curve does not follow a simple reverse course, but its final form is similar to the control.

In the case of the *ventricular complex* the principal change in the early stages of the action of the drug is as a rule marked inversion of the regression process with great increase in amplitude (Fig. 3c). The early ventricular effects are not so constant as in the auricle, probably because of the more complicated way in which the impulse spreads over this chamber. The regression deflection almost always increases in magnitude but is sometimes upright instead of inverted (Fig. 1).

The shortening of the duration of electrical systole suggests that the refractory period may be similarly shortened. Very accurate measurements are impossible when the effect of the drug is, as in this case,

transient, and the duration of electrical systole is almost constantly changing. By repeated trials it was possible, however, to obtain satisfactory estimates. Two experiments, one on an auricle and one on a ventricle, are summarized in Fig. 4. The duration of the refractory period shortens *pari passu* with that of electrical systole, but is always somewhat shorter.

In the process of ascertaining the length of the refractory period an early stimulus often gave rise to multiple responses or to paroxysms of fibrillation or flutter (Fig. 5*a* and *b*). Such responses rarely occurred in normal hearts but were almost universal when hearts were under the

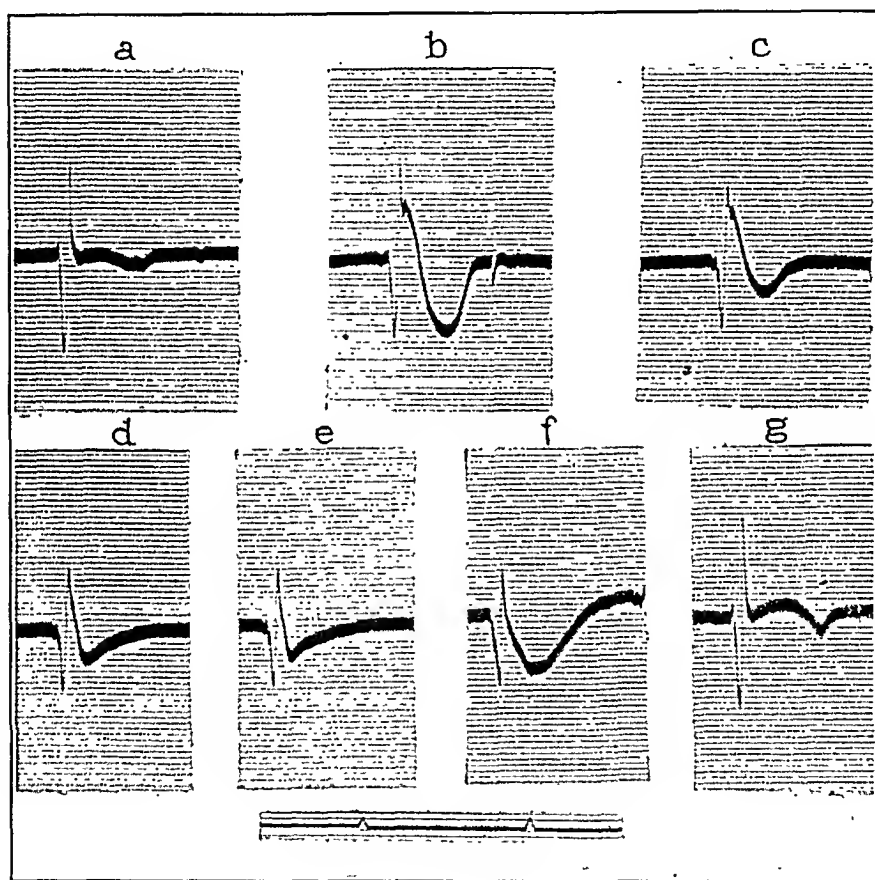


Fig. 2.—Electrograms from the center of the anterior surface of the frog's auricle after auriculoventricular heart block was produced by Stannius' ligature. The auricular complexes are seen by themselves.

<i>a</i> , before administering any drug	$\lambda_a = 0.59$ second
<i>b</i> , 30 seconds after 0.1 e.c. of acetyl-beta-methylcholine solution (0.01 mg./e.c.) intravenously	$\lambda_a = 0.53$ second
<i>c</i> , 1½ minutes after injection intravenously	$\lambda_a = 0.47$ second
<i>d</i> , 2½ minutes after injection intravenously	$\lambda_a = 0.46$ second
<i>e</i> , 15 minutes after injection intravenously	$\lambda_a = 0.41$ second
<i>f</i> , 18 minutes after acetyl-beta-methylcholine and 30 seconds after 0.2 e.c. of atropine solution (1.0 mg./e.c.)	$\lambda_a = 0.64$ second
<i>g</i> , 5 minutes after atropine injection	$\lambda_a = 0.61$ second

influence of acetyl-beta-methylcholine. Aberrant rhythms frequently occurred spontaneously in auricles (Fig. 1*d*) while they were under the influence of the drug, but were observed in ventricles only following an early stimulus (Fig. 5*b*).

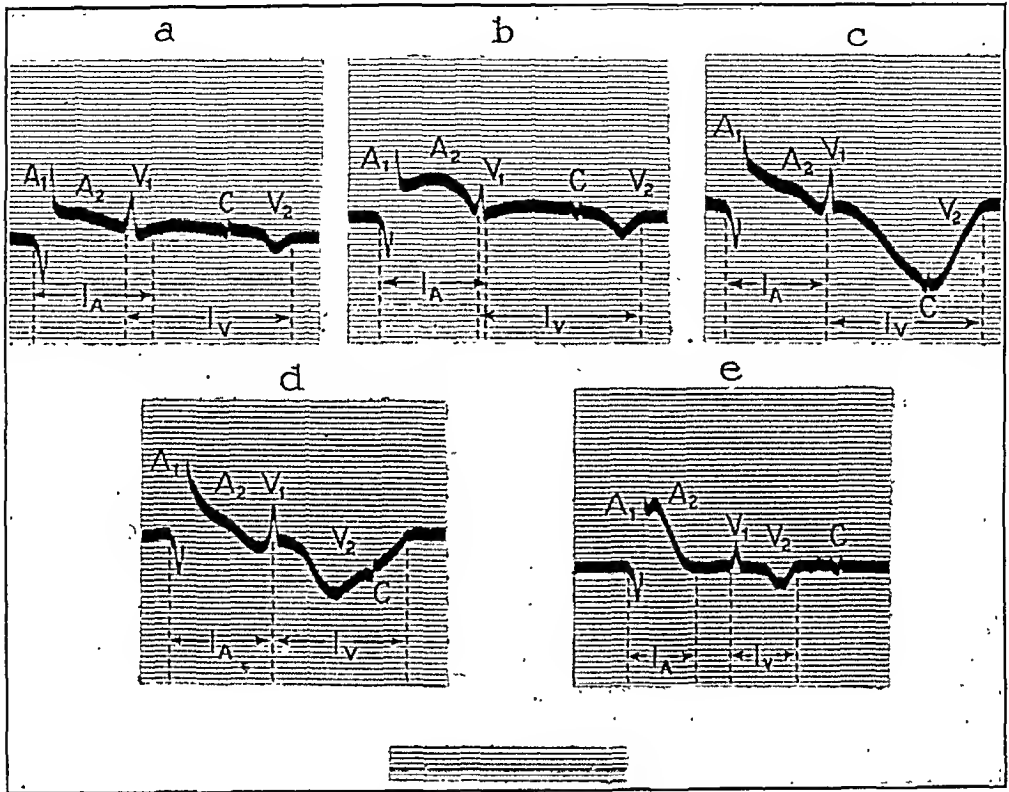


Fig. 3.—Electrograms from center of anterior surface of frog's auricle similar to those in Fig. 1, but showing more typical changes in the ventricular regression deflection V_2 , but very slight change in conduction time. 0.2 e.c. of acetyl-beta-methylcholine solution (0.01 mg./c.c.) was injected intravenously between *a* and *b*. The letters denote the same entities as in the previous figure.

CURVE	l_A SEC.	l_V SEC.	A-V INTERVAL	A-C INTERVAL
<i>a.</i> control	0.69	1.00	0.53	0.56
<i>b.</i> 9 seconds after injection	0.66	1.00	0.58	0.56
<i>c.</i> 16 seconds after injection	0.63	0.95	0.58	0.58
<i>d.</i> 24 seconds after injection	0.61	0.81	0.61	0.58
<i>e.</i> 61 seconds after injection	0.40	0.40	0.61	0.60

A few experiments were performed with acetylcholine instead of acetyl-beta-methylcholine. The results were identical except that a larger dose was required to produce the same effect.

DISCUSSION

Mines¹¹ described experiments on the effect of muscarine on frogs' hearts. He found that the duration of electrical systole and the force of ventricular contraction were reduced, but that auriculoventricular conduction was little changed. Because of the close relationship between muscarine, acetylcholine, and acetyl-beta-methylcholine, Mines's results and those reported in this paper may be considered corroborated.

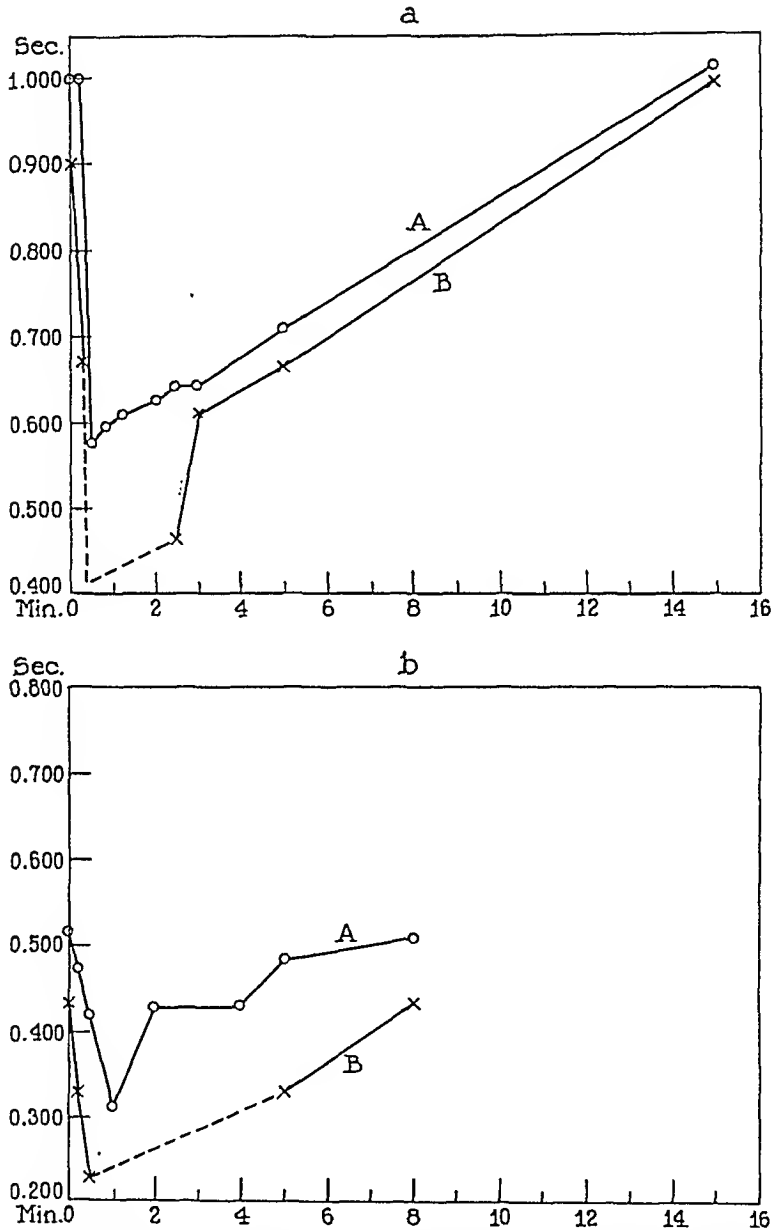


Fig. 4.—*a*, Graph of the effect of injecting 0.1 c.c. of acetyl-beta-methylcholine solution (0.01 mg./c.c.) intravenously on the duration of the electrical response and the refractory period of the frog's ventricle. Curve A is the effect on the duration of the electrical response, and curve B the effect on the refractory period (the dotted portion of the curve is hypothetical).
Ordinates are the duration of the process in seconds.
Abscissas are the times after injection in minutes.
b, The effect of injecting 0.15 c.c. of acetyl-beta-methylcholine on the auricle. Curve A is the duration of the electrical response and curve B the length of the refractory period.

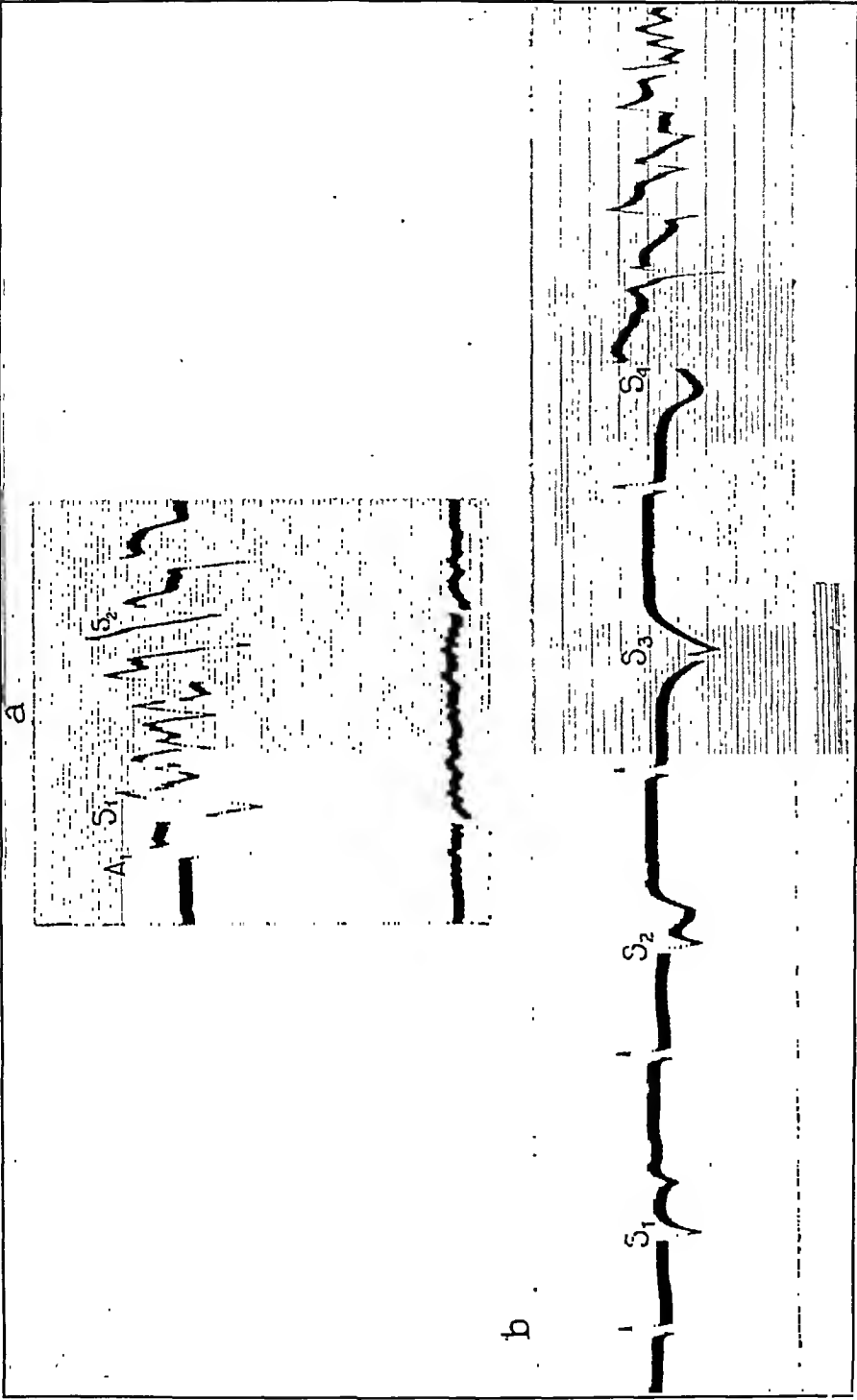


Fig. 5.—Fibrillation produced by a stimulus falling shortly after the end of the absolute refractory period in a heart under the influence of acetyl-beta-methylcholine.
a, fibrillation of the auricle; *S*₁ and *S*₂ are stimuli.
b, fibrillation of the ventricle; *S*₁, *S*₂, *S*₃ are stimuli (this curve also shows the development of the effect on *V*₂).

tory. Mines noticed that muscarine did not occasion heart block. This observation has interest because this is the outstanding regard in which acetyl-beta-methylcholine fails to imitate vagus stimulation. As is well known, stimulating the vagi almost invariably produces prolongation of the auriculoventricular interval and, indeed, frequently causes partial or complete dissociation. But in none of the experiments of the present study was there ever more than a slight increase in the time of auriculoventricular conduction. The failure of these drugs (cholines) to be vagomimetic in this respect when given intravenously may depend on anatomic peculiarities of the frog's heart. Except the conus, no part of the frog's heart, as Grant and Regnier¹² have shown, is supplied with arteries; following injection into the blood stream, therefore, the drug reaches the myocardium by simple diffusion. Since the auriculoventricular bundle is embedded in tissue and is therefore removed from immediate contact with the blood stream, it is not directly reached by drugs. The sinus, on the other hand, is a thin structure not much covered over, so that it is very quickly acted on and exhibits the earliest effect of the drug in the form of sinus brachycardia or asystole. It is possible that the failure of these drugs to produce heart block is caused, therefore, not by their inability to affect the auriculoventricular tissue, but by their failure to reach it.

Heat, increase in rate of stimulation, and the drugs of the digitalis group⁸ are also capable of shortening electrical systole and in some instances of producing aberrant rhythms. Since so many physiologic functions have already been ascribed to acetylcholine, the question arises: Do any or all of these agencies act through the instrumentality of this substance? In the case of heat it is unlikely that shortening of the regression process is anything other than acceleration of the chemical reactions which bring about recovery. The progressive decrease in the duration of electrical systole and the refractory period with increase in the rate of stimulation is an interesting phenomenon for which no satisfactory explanation has been offered. The phenomenon in many ways resembles the effect of acetylcholine, but differs from it in that it is not abolished or opposed by atropine. The shortening caused by the digitalis drugs is also not antagonized by atropine. Acetylcholine or a closely related compound does not therefore seem to play a role in any of these phenomena.

In most of the experiments in this study the electrodes were arranged to record the events in both auricle and ventricle, and to bring out their time relationships rather than the form of the auricular electrogram. Curves such as those in Fig. 2 can, however, be compared fairly with those reported by Macleod¹⁰ in his study of the form of the electrogram and its relation to the fundamental processes in cardiac muscle. The course of events in this experiment resembles that which he observed on

the application of heat, but there are certain irregularities which require explanation. Particularly noticeable is the regression deflection of Fig. 2f, which may have been expected to resemble Fig. 2b but, instead, is almost monophasic. In attempting an explanation of this divergence from the expected form it is necessary to recall the conditions which must be fulfilled in order to obtain electrograms which correspond to Macleod's theoretic curves. In constructing these hypothetic curves only the existence of a narrow strip of muscle was assumed, with the excitation process travelling from one end towards the other. The curves obtained from a narrow strip resemble those from a wide one (the auricle) only if the duration of systole is the same for every muscle element and the speed with which the process travels is uniform throughout the muscle. If the duration of the excited state differs in different regions the curve may be greatly distorted. That the effect of the drug might persist much longer in some muscle elements than in others is easily possible, and would account for the failure of the curves to correspond to theoretic ones. It is in the transitional states during which the effect of the drug is increasing or decreasing that the most aberrant curves would occur. In a thin structure like the auricle, which is bathed uniformly with blood over one entire surface, absorption may be uniform, but the decay of the action depending on a number of factors would scarcely be the same for all regions.

The tendency of meclohyl to usher in fibrillation or flutter is the result of its effect upon the refractory period. Since Lewis⁴ has discussed this relationship (the reduction of the refractory period and the occurrence of aberrant rhythms) at length, it need not be repeated here.

If the chief effect of acetyl-beta-methylcholine resembles that of the digitalis glucosides (a shortening of electrical systole), the two drugs may be expected to produce similar effects upon the human electrocardiogram. Page,¹³ in his report on its clinical effects, illustrated the electrocardiographic changes. In the case of the subject whose curves are illustrated the electrocardiogram was normal before the drug was given but, during the height of the action, inverted T-waves, similar to those which digitalis produces, developed. The effect was, of course, transient, and the curve quickly returned to normal.

SUMMARY

Acetyl-beta-methylcholine shortens the duration of electrical systole and the refractory period in the frog's heart. In consequence, it may induce aberrant rhythms. These effects are abolished by atropine. Its failure to produce heart block is strange, but this can be explained on the basis of anatomic peculiarities of the frog's heart. It is probable that similar effects produced by frequent stimulation and the digitalis glucosides are not mediated by acetylcholine. Like the digitalis drugs,

and probably by a similar mechanism, mecholyl causes inversion of the T-wave of the human electrocardiogram.

REFERENCES

1. Gaskell, W. H.: On the Rhythm of the Heart of the Frog, and on the Nature of the Action of the Vagus Nerve, *Phil. Tr. Roy. Soc. London*, 172: Part 3, 993, 1882.
2. Engelmann, T. W.: Ueber primär-chronotrope Wirkung des Nervus vagus auf das Herz. *Cinquanteuaine Soc. Biol.*, p. 86, Paris, 1899, Masson.
3. Mines, G. R.: Further Experiments on the Action of the Vagus on the Electrogram of the Frog's Heart, *J. Physiol.* 47: 419, 1913.
4. Lewis, T., Drury, A. N., and Bulger, H. A.: Observations Upon Flutter and Fibrillation. Part VII. The Effect of Vagal Stimulation, *Heart* 8: 141, 1921.
5. Lewis, T., Drury, A. N., and Ilescu, C. C.: Further Observations Upon the State of Rapid Re-Excitation of the Auricles, *Heart* 8: 311, 1921.
6. Robinson, G. C.: The Influence of the Vagus Nerves on the Faradized Auricles in the Dog's Heart, *J. Exper. Med.* 17: 429, 1913.
7. Goldenberg, M., and Rothberger, C. J.: Über die Wirkung von Acetylcholin auf das Warmblüterherz, *Ztschr. f. d. ges. exper. Med.* 94: 151, 1934.
8. Fredericq, H.: Altérations de l'électrogramme auriculaire de la Tortue, produites par une excitation isolée du nerf pneumogastrique. *Compt. rend. Soc. biol.* 108: 422, 1931.
9. Macleod, A. G.: The Effect of Certain Digitalis-Like Glucosides on the Frog's Heart, *AM. HEART J.* 17: 294, 1939.
10. Macleod, A. G.: The Electrogram of Cardiac Muscle. I. An Analysis Which Explains the Regression or T Deflection, *AM. HEART J.* 15: 165, 1938.
11. Macleod, A. G.: The Electrogram of Cardiac Muscle. II. The Lengths of the Stages of Activity, *AM. HEART J.* 15: 402, 1938.
12. Mines, G. R.: On the Action of Muscarine on the Electrical Response of the Heart, *J. Pharmacol. Exper. Therap.* 5: 425, 1913-14.
13. Grant, R. T., and Regnier, M.: The Comparative Anatomy of the Cardiac Coronary Vessels, *Heart* 13: 285, 1926.
14. Page, I. H.: Acetyl-beta-Methylcholin (Mecholin). Observations Concerning Its Action on the Blood Pressure, Skin Temperature and the Heart, as Exhibited by the Electrocardiogram. *Am. J. M. Sc.* 189: 55, 1935.

THE TREATMENT OF DEEP THROMBOPHLEBITIS AND CHRONIC LEG ULCERS WITH ACETYL-BETA-METHYL- CHOLINE CHLORIDE IONTOPHORESIS

RAYMOND A. SOKOLOV, M.D., AND MAURICE P. MEYERS, M.D.
DETROIT, MICH.

ACETYLCHOLINE was shown by Dale¹ to be the chemical substance released upon stimulation of the parasympathetic nerve endings. This substance proved too unstable to be of therapeutic value. Major and Cline² prepared a more stable compound, acetyl-beta-methylcholine chloride (mecholy); the latter has an action similar to acetylcholine and can be administered orally, subcutaneously, and by iontophoresis. The action of the drug on parasympathetic nerve endings was utilized in patients in whom it was desirable to cause peripheral vasodilatation. To ensure a concentrated local effect and to avoid undesirable general effects of the drug,³ Kovacs⁴ attempted to use this agent by ionization through the unbroken skin. He found the treatment to be of value in chronic arthritis, especially in the rheumatoid type, and also in peripheral vascular disease in which spasm was an important factor. Employing the same technique, Saylor, Kovacs, Duryee, and Wright⁵ found the treatment to be effective in the healing of chronic varicose ulcers. In attempting to reproduce these results in treating chronic ulcers in this clinic it was noted that in cases in which there was a co-existing deep thrombophlebitis iontophoresis caused improvement in the symptoms of the latter condition as well as healing of the ulcers. This led to the use of acetyl-beta-methylcholine chloride* iontophoresis in cases of deep thrombophlebitis without ulcers. While this work was in progress Murphy⁶ reported favorable results with similar treatment in a series of thirty-three cases of thrombophlebitis, though he did not distinguish between superficial and deep thrombophlebitis.

In this study are included nineteen cases of thrombophlebitis of deep veins and thirteen cases of chronic leg ulcers of various etiology. Some of the patients were from the outpatient department, while others were private patients referred to the peripheral vascular department of the hospital. The great majority, by far, were ambulatory.

The technique of the treatment was essentially the same as that of Kovacs⁴ (for a detailed description of it the reader is referred to his article). It was found that a 0.1 per cent solution of acetyl-beta-methylcholine chloride was as effective as the higher concentrations previously recommended. The individual treatments were as

From the Peripheral Vascular Clinics of Harper Hospital and the North End Clinic, Detroit, Michigan.

*The acetyl-beta-methylcholine chloride (Mecholy) used in this study was kindly supplied by Merck and Company of Rahway, N. J.

Received for publication Aug. 15, 1938.

a rule of forty-five minutes' duration. The first six to ten treatments were given at daily intervals. These were subsequently reduced to two to three weekly, as improvement permitted.

No untoward general effects from the treatment were observed in this group of cases. The side effects noted were the same as those reported by others, namely, local diaphoresis, flushing, salivation, and occasionally increased intestinal peristalsis. Two patients unfortunately sustained small eschars of the legs following iontophoresis therapy. The difficulty was traced to a faulty galvanic machine. After abandoning the use of that particular machine, this problem was not again encountered. The eschars responded well to simple measures.

THROMBOPHLEBITIS OF DEEP VEINS

In this study cases of superficial phlebitis or phlebitis of varicose veins have not been included. Individual episodes of superficial phlebitis tend to be self-limited and do not constitute as formidable a therapeutic problem as do the chronic lymphedemas secondary to deep thrombophlebitis. We are concerned here with the nonsuppurative postoperative or postparturient phlebitis, known under the various names of milk leg, phlegmasia alba dolens, or postphlebitic edema. This lesion usually is seen following abdominal operations or septic deliveries, though it may occur after trauma, septicemia, and generalized infections; moreover, cases of so-called idiopathic thrombophlebitis have been reported.⁷ In one case in this present group the phlebitis followed a severe burn of the leg.

The onset of the condition is frequently announced by a rise in pulse rate and temperature, often with chill. The patient may complain of pain or stiffness in the leg or behind the knee, or difficulty in moving the leg. Shortly afterward the limb begins to swell. In the milder cases the swelling may disappear in a short time; in the more severe cases the swelling persists for several months and may become permanent. In these more unfavorable cases the skin becomes thickened, infiltrated, and brownly pigmented; the leg becomes heavy, painful, and practically useless. Later sequelae take the form of dermatoses, indurations, and ulcerations, which add materially to the distress of the patient.

Two opposing explanations have been offered as to the cause of this postphlebitic edema: One stresses interference with venous return,⁸ the other attributes the edema to lymph stasis resulting from concomitant involvement of the lymph channels with the perivenous inflammatory reaction.⁹ Whichever of these may be the correct interpretation, there are certain factors which are known to favor the formation of thrombi. Chief among these is slowing of the rate of blood flow, which can be a consequence of surgical anesthesia, prolonged inactivity during convalescence, advanced age, and perhaps hypothyroidism. Other factors are change in blood volume due to dehydration and hemorrhage, presence of infection or febrile reaction, trauma, and possibly some not well understood changes in blood coagulation factors and in blood chemistry.

The greater frequency of involvement of the left side has been explained on the basis of anatomic variations of the iliae veins on the two sides; the left common iliae vein is longer and more oblique than the right and is pressed upon by the right common iliae artery and by the adjacent portion of the colon, all of which favor venous stasis.

The treatment of postphlebitic edema has until very recently been far from satisfactory. Elastic supports, massage, heat, and light are therapeutic gestures and nothing more, in many cases. The Kondoleon operation is a formidable procedure. Extract of leeches has been advocated in this condition, but little is yet known of its value.¹⁰ The use of acetyl-beta-methylcholine chloride iontophoresis in deep thrombophlebitis seemed to be a more satisfactory method of treatment than others previously suggested.

Nineteen patients with thrombophlebitis of deep veins have been treated by this method; the results are recorded in Table I. The shortest duration of the disease among the patients treated was eight days, the longest thirty-two years. Three patients were treated while they were still in the hospital recovering from their respective operations; these patients whose phlebitis was subacute were kept at rest in bed until improvement was well advanced. The remaining patients, who came to us after the condition had been present for several months or more, were easily managed while they were ambulatory. Of this latter group it was necessary to hospitalize only one individual; he lived a long distance from the clinic and found it difficult to come back and forth for treatment.

Improvement was noted in eighteen of the nineteen cases. The majority of the patients were able to return to full-time work, some at hard manual labor. Others were only partially rehabilitated. In one patient pain and disability, which had been present for thirty years, completely disappeared. Many of the patients had had various other forms of treatment over a period of years without relief.

Most marked improvement was noted in instances in which the disease was of not too long standing. When the disease had been present for a number of years improvement was slow and less dramatic. It is advisable to warn the patient that improvement may not manifest itself until several treatments have been given, else he may become discouraged and cease reporting for further therapy. It is not unusual, especially in the cases of old chronic phlebitis, to see no alteration in the disease process until a considerable period of time has elapsed, and then suddenly to observe beneficial changes taking place. In fresh postoperative cases the results were at times quite dramatic.

Criteria of improvement were (1) diminution in the size of the limb as determined by measurements taken circumferentially at the level of the largest diameter of the calf and at the level of the malleoli; (2) im-

provement in ability to walk and stand; (3) ability to resume previously impossible occupations or tasks; (4) freedom or relief of subjective symptoms such as pain, heaviness of the legs, or "stiffness" of the legs. In Table I the results are recorded in greater detail. The degree of disability in each case was graded + to +++++. Grade + signified swelling without discomfort, ++ swelling plus mild disability, +++ extensive edema plus severe disability, +++++ total disability and confinement to bed. The relative amount of improvement was likewise graded, ranging from +, which represented slight improvement, to +++++, which signified complete cure.

There are many victims of deep thrombophlebitis suffering from varying degrees of disability. As a rule these people are resigned to their fate, after having submitted themselves to a number of therapeutic efforts over a period of years without result. With the introduction of iontophoresis therapy with acetyl-beta-methylcholine chloride a good percentage of the people treated have had relief of distress and decrease in swelling of the affected limbs. They have been able to resume previous occupations or household tasks which they had given up because of their illness.

CHRONIC LEG ULCERS

Saylor and his co-workers observed good results in the treatment of chronic varicose ulcers following the use of acetyl-beta-methylcholine chloride iontophoresis.⁵ In this study the same method was used in the treatment of varicose ulcers and also for ulcers of other etiology. The results are recorded in Table II. In several cases the etiology was indefinite or possibly multiple; in at least four instances there was an underlying peripheral arterial deficiency. Two were pyogenic ulcers, three were varicose ulcers. It was found in this small group that the treatment was apparently as effective in healing leg ulcers of other than varicose vein etiology as it was in the treatment of varicose ulcers. In many instances the patients had had previous therapy of various sorts without improvement. In general, no other form of treatment was used concurrently with the administration of the iontophoresis. There were some exceptions. One patient, who had cardiac failure with peripheral edema, was kept completely at rest in bed and given appropriate therapy. In three cases, in which the ulcer was associated with an abundant purulent discharge, urea crystals were applied locally until the exudation ceased.

One precaution which is observed in treating open skin lesions by the method of iontophoresis is that the ulcerated area itself is covered with a thin piece of rubber sheeting. If this is neglected there is likely to be concentration of the current at the point of ulceration, which may cause pain and further tissue destruction.

TABLE
DEEP THROMBOPHLEBITIS TREATED

NO.	PATIENT	AGE & SEX	LESION	DURATION	DISABILITY	ETIOLOGY
1	S. W.	47 F	Chronic thrombo- phlebitis (deep), left leg.	6 years	+++	Pelvic operation
2	G. G.	59 M	Chronic thrombo- phlebitis (deep), bilateral.	9 years	+++	Cholecystostomy
3	G. D.	56 F	Subacute thrombo- phlebitis (deep), left leg.	8 days	++++	Cholecystectomy
4	A. S.	60 F	Chronic thrombo- phlebitis (deep), bilateral.	32 years	++	Childbirth
5	W. R.	32 M	Subacute thrombo- phlebitis (deep), left leg.	1 month	++	Herniorrhaphy
6	B. M.	39 F	Subacute thrombo- phlebitis (deep), left leg.	6 months	++	Herniorrhaphy
7	A. G.	45 F	Chronic thrombo- phlebitis (deep), left leg.	30 years	+++	Ankle injury
8	E. B.	33 M	Chronic thrombo- phlebitis (deep), right leg.	3 years	+++	Leg injury, septicemia
9	W. K.	65 M	Subacute thrombo- phlebitis (deep), right leg.	3 months	++	Gangrenous appendi- citis
10	F. C.	36 F	Chronic thrombo- phlebitis (deep), bilateral.	right 8 years left 3 years	+++	Septic abortion, childbirth
11	H. S.	39 F	Subacute thrombo- phlebitis (deep), bilateral.	13 days	+++	Pelvic operation
12	W. F.	35 M	Chronic thrombo- phlebitis (deep), left leg.	8 months	+++	Burn
13	F. B.	54 M	Chronic thrombo- phlebitis (deep), right leg.	3 months	+++	Indefinite
14	G. G.	51 M	Chronic thrombo- phlebitis (deep), bilateral.	2 months	+++	Herniorrhaphy
15	H. W.	43 F	Chronic thrombo- phlebitis (deep), bilateral.	18 years	+++	Childbirth
16	E. F.	45 F	Chronic phlebitis (deep), right leg.	23 years	++	Childbirth
17	J. A.	46 M	Chronic thrombo- phlebitis (deep), bilateral.	28 years	+++	Typhoid fever
18	H. P.	44 F	Chronic thrombo- phlebitis (deep), left leg.	19 years	++	Childbirth
19	S. H.	46 F	Chronic thrombo- phlebitis (deep), left leg.	14 years	++	Childbirth

I
BY IONTOPHORESIS WITH MECHOLYL

DURATION OF TREATMENT	NUMBER OF TREATMENTS	RESULT	QUANTITATIVE RESULT	REMARKS
2 months	27	Improved	+++	Measurements decreased; no pain; moderate swelling toward evening. Now holds full-time job.
4 months	60	Improved	+++	Measurements decreased; walks well. Still has occasional pain.
3 weeks	18	Improved	+++	Measurements decreased; little or no swelling, walks normally.
26 days	15	Improved	+	Measurements improved, leg softer, walking better.
9 days	8	Improved	+++	Measurements improved; has only slight ankle edema after hard day's work.
2 months	22	Improved	+++	Measurements improved; able to do all her housework.
7 weeks	24	Improved	+++	Measurements decreased, pain disappeared completely.
6 weeks	39	Not Improved	0	
7 weeks	31	Improved	+++	Now has only slight swelling of ankles after full day's work.
3 months	29	Improved	++	Ulcers healed, swelling partially reduced, able to do housework.
3 weeks	18	Cured	++++	No swelling; no symptoms.
6 weeks	32	Improved	++	Measurements decreased, no pain, walks better.
5 weeks	12	Improved	+++	Measurements reduced, no pain, walks without difficulty.
6 months	63	Improved	++	Left leg became normal, right leg only partially improved.
4 weeks	11	Improved	+++	Swelling reduced, walking improved.
6 weeks	21	Improved	+++	Less swelling, no pain, able to do all her housework.
4 weeks	12	Improved	+++	Measurements decreased, improved ability to walk.
2 weeks	7	Improved	+++	Measurements decreased, no pain, now able to do all her housework without difficulty.
6 weeks	12	Improved	++	

TABLE
TREATMENT OF CHRONIC LEG ULCERS

NO.	PATIENT	AGE & SEX	LESION	DURATION	DISABILITY	ETIOLOGY
1	A. L.	42 F.	Chronic ulcer of foot	4 months	+++	Raynaud's disease with scleroderma
2	N. P.	23 M	Chronic purulent ulcer of leg	20 months	+++	Osteomyelitis of right tibia
3	B. L.	74 F	Ulcer due to stasis plus arterio-sclerosis	3 weeks	++++	Cardiac insufficiency with peripheral edema; arteriosclerosis
4	J. M.	46 M	Ulcer of foot	5 months	+++	Diabetes
5	F. F.	41 F	Ulcer of ankle	4½ years	+++	Varicose veins
6	E. G.	50 F	Ulcer of ankle Chronic ulcer of leg	15 years	++	Varicose veins
7	T. H.	36 F	Boeck's sarcoid (?)	2 years	++	Indefinite
8	F. W.	52 M	Chronic leg ulcer	5 years	+	Microscopic examination inconclusive: (1) tuberculosis, (2) probable syphilis
9	F. T.	33 F	Chronic ulcers of left ankle	2½ years	++	Fracture
10	R. G.	47 F	Ulcer of right thigh	7 months	+	Abscess following insulin injection, diabetes
11	H. K.	45 M	Ulcer of left ankle	20 months	+	Indefinite: old fracture, syphilis, nephritis
12	M. S.	26 M	Ulcer of toe	1 month	++	Diabetes
13	H. H.	39 M	Chronic ulcer— medial aspect left ankle	4 months	++	Varicose veins

Clinical improvement in these ulcer cases was manifested shortly after treatment was started. After two or three applications a healthy red granulation tissue appeared at the base of the ulcer. Soon growth of epithelium became evident at the border, and by the end of six or seven days measurable differences in the size of the lesions were apparent.

Though the limitations of drawing conclusions from such a small series of cases are recognized, the results were so uniformly good that it seemed worth while to report them.

II

BY IONTOPHORESIS WITH MECHOLYL

DURATION OF TREATMENT	NUMBER OF TREATMENTS	RESULT	QUANTITA- TIVE RESULT	REMARKS
3 weeks	14	Healed ulcer	++++	Previously treated by bed rest and ointments without improvement.
5½ months	79	Healed ulcer	++++	Previous to treatment, ulcer was becoming progressively worse. Urea crystals used until purulent discharge ceased.
5 weeks	30	Healed ulcer	++++	Urea crystals and bed rest also employed.
3 months	17	Healed ulcer	++++	
3 weeks	17	Healed ulcer	++++	Had previously had Unna boot, elastic supports, ointments, and ultraviolet light.
5 weeks	21	Healed ulcer	++++	
1 month	28	Healed ulcer	++++	
6 weeks	17	Healed ulcer	++++	Ulcer previously treated in 2 other clinics.
5 weeks	14	Ulcers healing	+	
15 weeks	36	Ulcer healed	++++	Ulcer healed after treatments, but discharge continued 5 months.
7 weeks	13	Ulcer healed	++++	No improvement with Unna boot, nor with anti-syphilitic therapy.
6 weeks	14	Ulcer partially healed	++	Completely healed only after 5 months and after patient was put to bed.
6 weeks	15	Healed ulcer	+++	Had previously had vein ligations and supportive bandages, plus various types of ointments.

SUMMARY

Iontophoresis with acetyl-beta-methylcholine chloride was used in the treatment of nineteen patients with deep thrombophlebitis with good results in eighteen cases. The same form of therapy was employed in thirteen cases of chronic leg ulcers of various etiology; these ulcers had completely healed in twelve cases, and in the thirteenth the lesion was healing rapidly when last observed.

We are grateful to Dr. Hugo A. Freund for his permission to investigate and report those cases in which treatment was carried out under his direction at Harper Hospital, and to Dr. Saul Rosenzweig for his cases at North End Clinic.

REFERENCES

1. Dale, H. H.: Croonian Lectures on Some Chemical Factors in Control of Circulation, *Lancet* 1: 1285, 1929.
2. Major, R. T., and Cline, J. K.: Preparation and Properties of Alpha and Beta-Methylcholine and Gamma-Homocholine, *J. Am. Chem. Soc.* 54: 242, 1932.
3. Starr, I., Jr., Elsom, K. A., Reisinger, J. A., and Richards, A. N.: Acetyl-Beta-Methylcholin. I. The Action on Normal Persons, *Am. J. M. Sc.* 186: 313, 1931.
4. Kovacs, Joseph: The Iontophoresis of Acetyl-Beta-Methyl Choline Chloride in the Treatment of Chronic Arthritis and Peripheral Vascular Disease. Preliminary Report, *Am. J. M. Sc.* 188: 32, 1934.
5. Saylor, L., Kovacs, J., Duryee, A. W., and Wright, I. S.: The Treatment of Chronic Varicose Ulcers by Acetyl-Beta-Methyl Choline Chloride Iontophoresis, *J. A. M. A.* 107: 114, 1936.
6. Murphy, Hugh L.: The Treatment of Thrombophlebitis With Acetyl-Beta-Methyl Choline Chloride Iontophoresis, *Surg., Gynec. & Obst.* 65: 100, 1937.
7. Barker, Nelson W.: Primary Idiopathic Thrombophlebitis, *Arch. Int. Med.* 58: 147, 1936.
8. Zimmerman, L. M., and de Takats, G.: The Mechanism of Thrombophlebitic Edema, *Arch. Surg.* 23: 937, 1931.
9. Homans, J.: Thrombophlebitis of the Lower Extremities, *Ann. Surg.* 87: 641, 1928.
10. Petrov, I. R., et al.: Experimental and Clinical Studies on Therapy of Thrombophlebitis With Extract of Leeches, *Vestnik Khir.* 47: 163, 1936.

PAPAVERINE HYDROCHLORIDE

ITS QUESTIONABLE VALUE AS A VASODILATING AGENT FOR USE IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASES

DAVID LITTAUER, M.D., AND IRVING S. WRIGHT, M.D.
NEW YORK, N. Y.

AS PART of the present trend toward conservatism in the treatment of diseases of the peripheral circulation, several pharmaceuticals with vasodilating properties, notably histamine, acetylcholine, acetyl-beta-methyl choline, theobromine sodium salicylate, and tissue extracts, have come into popular use. With increasing experience, certain of these substances have been found to possess, at most, limited usefulness. In the last few years papaverine, a member of the isoquinoline group of opium alkaloids, has been widely recommended as a rapidly acting vasodilator because of its relaxing effect on smooth muscle.

Papaverine was first identified among the alkaloids of opium by Merck, in 1848.² Its formula was worked out by Goldschmidt² about forty years later, and in 1909 it was prepared synthetically by Pictet and Gans.² A preparation closely related chemically to papaverine, and used especially in Europe, is eupaverine,³ which is claimed to be less toxic but is also less soluble than papaverine. Pal, who has done considerable experimental work with papaverine on animals and to a lesser extent on man,^{4a-c} has concluded that the drug has the property of relaxing smooth muscle throughout the body by local action on the muscle fibers. If this is true, it should produce dilatation of blood vessels; in normals he found this relaxing effect to be insignificant, while if vasoconstriction has been produced by administration of adrenalin the relaxing effect is much greater. Pal's findings have been confirmed in a general way by Renon and Desbouis,⁵ Adler,⁶ and Macht.⁷ The latter made an extensive pharmacologic study on animals of the effects of the drug on the circulation, on respiration, on smooth muscle, and as an analgesic. He found that papaverine causes marked dilatation of the coronary, splanchnic, and peripheral arteries; it causes a slight decrease in the rate of respiration, but a marked increase in volume output and alveolar ventilation, and also dilates the bronchi; it relaxes smooth muscle without paralyzing it; and as an analgesic it is more effective than codeine but less effective than morphine. Barlow⁸ has confirmed its inferior potency as a sedative and as an inhibitor of spontaneous movements in the rat.

Gruber and Robinson⁹ have shown that in the perfused mammalian heart papaverine hydrochloride causes considerably greater dilatation

From the Vascular Clinic of the Department of Medicine, New York Post Graduate Hospital, and the Medical School of Columbia University.

Received for publication Aug. 15, 1938.

of coronary vessels than does morphine, although only one-tenth the dose was used. Mercier¹⁰ found that the initial fall in blood pressure following the action of papaverine on the smooth muscle fibers is succeeded by a rise, which he attributed to vasoconstriction.

The tonus of the smooth muscle of the intestinal tract is usually decreased by papaverine injected intravenously, although sometimes increased peristalsis may result, according to Gruber and Robinson¹¹ and Gruber and Brundage.¹² Samaan¹³ also has found it effective in relieving intestinal spasm. However, Gross and Slaughter¹⁴ claim that as a relaxer of smooth muscle in the gastrointestinal tract papaverine is effective only on the musculature of the stomach, and that its effect is slight compared to the similar action of morphine.

Samaan¹⁵ has reported favorably on the relaxing effect of papaverine and eupaverine on the smooth muscle of the genitourinary and biliary tracts.

Clinically, this relaxing property of papaverine has prompted its use in acute uremia,^{4d} angina pectoris, bronchial asthma, and dysmenorrhea.^{4a} In the last three years several reports have appeared on the effectiveness of papaverine in releasing the vascular spasm accompanying acute embolism or thrombosis of the vessels of the extremities. Denk,^{16a, b} using eupaverine in doses averaging 0.03 to 0.06 gm. ($\frac{1}{2}$ to 1 gr.) intravenously every few hours, reports that in twenty-five cases of acute embolism of major vessels of the extremities there was complete restoration of circulation in seventeen, improvement in three, and no favorable effect in only five. His criteria of improvement are based on clinical findings and capillary microscopy. He concluded that these results are at least as good as are usually obtained with embolectomy, and the latter procedure can always be attempted if a trial with papaverine is ineffectual in a few hours.

Allen and MacLean¹⁷ report a case of a 50-year-old diabetic male who suffered occlusion of the lower portion of the right femoral artery and the left iliac artery. Following the administration of .016 gm. ($\frac{1}{4}$ gr.) of papaverine intravenously, the condition of the right leg returned to normal, whereas the left lower extremity became progressively worse and at operation the larger arteries and veins were completely thrombosed. Five additional cases have been added by de Takats.¹⁸ In two, no benefit resulted from the use of papaverine, possibly because of the length of the interval between the arterial occlusion and administration of the drug. One of the remaining three was a case of pulmonary embolism and should be discounted. Adjuvant therapy, such as suction-pressure and a heat-regulated cradle, was used in the two cases in which improvement occurred.

In the experimental work on animals mentioned above, the results of competent observers were by no means uniform. In the small amount of clinical observation thus far reported, conditions were usually far from controlled. In some cases adjuvant therapy was employed. It is a

familiar clinical observation, moreover, that in many cases of acute embolism or thrombosis of a major artery of an extremity spontaneous recovery following ordinary symptomatic therapy, like warmth, sedatives, and analgesics, is the rule. This is especially true of nonseptic emboli in people under 45 years of age.

We therefore decided to investigate the effectiveness of papaverine as a vasodilator in cases of vascular disease in which measurable amounts of spasm, as determined by a standard procedure for securing vasodilatation, were known to exist. To this end a series of patients with various vascular syndromes, as well as two normal individuals, were subjected to a method of producing reflex vasodilatation with which we have had considerable experience. By this method we could demonstrate the capacity for vasodilatation in certain of the extremities selected for study. At subsequent sittings the same individuals were given papaverine in doses which were recommended therapeutically, and also in larger doses. In addition, we had the opportunity during the past year to observe six patients who were admitted to the hospital for sudden peripheral embolism or thrombosis and given papaverine within a short time after the vascular insult.

METHOD

Twenty-two subjects were studied, including thirteen with thromboangiitis obliterans, three with arteriosclerosis obliterans, four with Raynaud's syndrome, and two normal individuals free from vascular disease.

All were first tested with the procedure commonly used in our clinic to determine the possibility of reflex dilatation of the vessels of the extremities, namely, the hot water immersion test popularized by Landis and Gibbon.¹⁰ This compares favorably with other diagnostic tests for vasospasm, such as injection of the posterior tibial nerve and spinal or general anesthesia, except in cases of Raynaud's syndrome.

The procedure was as follows: The subject sat in a room free from drafts. The temperature was maintained between 20° and 22° C. (68°-71.5° F.). If the upper extremities were tested they were exposed from the elbows downward and the hands and forearms were rested on a table. Temperature readings of the skin of the dorsum of the first, third, and fifth digits of each extremity and of the dorsum of the foot (or hand) were taken by means of the Leeds and Northrup potentiometer with thermocouple junction of iron, copper, chromel, platinum rhodium (positive) and constantan, alumel and platinum (negative), and extension leads.

Readings were taken every ten minutes until stabilization of skin temperature had been achieved. In no instance were less than sixty minutes allotted to the period of stabilization, and in some cases ninety or more minutes were required.

After stabilization of skin temperature had occurred the opposite pair of extremities was immersed in surgical arm basins above the elbows (if upper extremities) or in deep pails to the knees (if lower extremities) containing water maintained at a temperature of 42° to 46° C. (107.5°-115° F.), and temperature readings of the extremities were made at five-minute intervals for thirty-five minutes.

Vasodilatation in a digit was not considered to have occurred unless there was a rise in the temperature of the skin of 2° C. (3.5° F.), or more, in at least two of the three digits from which readings were taken. Normal vasodilatation should produce a rise to above 30° C. (86° F.) in most individuals. A check on the effective-

ness of the procedure in producing vasodilatation of the superficial vessels of the entire body was the generalized sensation of warmth, diaphoresis, and flushing which would occur within five to fifteen minutes following immersion.

Each person was subjected at another sitting to the following procedure. Stabilization of the temperatures of the skin of the toes and feet was achieved. Blood pressure and pulse rate were also recorded during this period. Papaverine hydrochloride,* in the amount of 0.03 gm. (gr. $\frac{1}{2}$), was injected into an antecubital vein. Between thirty and forty-five minutes later the injection was repeated. For at least two hours following the initial injection the temperatures of the skin of the toes and feet were taken at ten-minute intervals, the pulse rate was counted every ten minutes, and the blood pressure was taken several times. In eleven cases the capillaries of the nailfold of a finger were also examined periodically under the microscope, before and after the injection of papaverine hydrochloride, for changes in size, shape, and rate of flow of the capillary stream. Changes in the color of the extremities and symptoms following the injections were also noted.

RESULTS

The classification of patients under the various diagnostic groups followed a thorough study in the Vascular Clinic. Patients with questionable diagnoses were not used in this work.

Patients With Thromboangiitis Obliterans.—Of the thirteen patients in this group, eight showed a significant response to the hot-water immersion test, the maximal rise in temperature of the toes ranging from 4.0° to 9.0° C. (7° to 16° F.) in different individuals. In each case in which a temperature rise occurred there was some degree of coincident improvement in the color of the toes, from rubor or dusky cyanosis to deep or light pink. Several patients remarked upon tingling or throbbing in the feet and toes.

In five subjects, a rise of temperature of at least 2° C. (3.5° F.) was not obtained. In this group there were some of our most advanced cases of thromboangiitis obliterans.

Following injections of papaverine, three of the thirteen members of this group exhibited a rise of skin temperatures and changes in color of the feet. Two of these had also responded to the hot-water immersion test, while the third had evinced no response to this test. The effect of papaverine hydrochloride on blood pressure, pulse rate, and capillaries is reviewed below.

Patients With Arteriosclerosis.—There were three patients in the group. One also had diabetes mellitus, controlled adequately by diet. Two exhibited no response to water immersion. Mid-thigh amputations for ischemia with gangrene of toes were subsequently performed on these two. In the third, excellent vasodilatation was obtained in one extremity and almost none in the other. In none of these patients was any rise in skin temperatures or changes in the color or feeling in the feet obtained following the intravenous injection of papaverine hydrochloride.

*Papaverine hydrochloride, Eli Lilly and Company, was used; 0.03 gm. is the maximum therapeutic dose recommended by several workers.

Patients With Raynaud's Syndrome.—There were four patients in this group. Tests for vasospasm and vasodilatation are admittedly unreliable in patients suffering from Raynaud's syndrome, and the studies were performed primarily to round out the group of common vascular disorders. Stabilization of temperatures is difficult to attain. Spontaneous release of spasm would occur at temperatures above 20.5° C. (69° F.). Readings in these patients, all of whom had marked involvement of the upper extremities, were taken from the finger tips and dorsi of the hands, the legs being immersed in a pail of warm water. One patient had scleroderma.

In two, rise of temperature of the fingers and change in appearance of the fingers from dead white or purplish cyanosis to healthy pink occurred following water immersion. In one no response was obtained. In the fourth it was impossible to secure constant readings, as the vasospasm came and went frequently. In all four cases papaverine had no vasodilating effect at the temperatures at which spasm could be maintained.

Normal Subjects.—Two normal controls were used. After stabilization of skin temperatures at a low level, elevation of temperatures to at least 30.5° C. (87° F.) in all toes was secured following water immersion. In neither case was any rise in the temperature of the toes elicited following injection of 0.06 and 0.10 gm. (1 and 1½ gr.), respectively.

Systemic Reactions Following Intravenous Injection of Papaverine Hydrochloride.—The majority of the twenty-two subjects studied had no symptoms following the intravenous injection of papaverine hydrochloride in so-called therapeutic doses. A few felt drowsy. One suffered momentary pain in the chest. One felt warm in the chest and abdomen; this sensation subsided after several minutes. A generalized sensation of warmth and throbbing in the temples occurred several hours after injection of 0.10 gm. (gr. 1½) in another. Blood pressure remained either unchanged or fell a few points. The maximal pulse rate variation, almost always in a downward direction in the cases in which it occurred, was ten beats per minute.

Examination of the capillaries of the nailbed of a finger before and after injection of papaverine hydrochloride was performed in the first eleven patients studied. In two who had Raynaud's syndrome the capillary picture changed without relation to the administration of the drug. In the other nine cases the size, shape, and rate of flow of the capillary stream were normal before injection and remained so. The capillaries of the toes could not be examined satisfactorily.

During the past year we have had the opportunity to observe four cases of acute peripheral embolism and two cases of thrombosis within a few hours after the accident. Five of these patients were given large doses of papaverine by mouth and intravenously, and the sixth received "spasmalgin," a proprietary preparation which contains papaverine,

but as we were not convinced of the efficacy of the drug alone, and saw no reason to withhold other therapeutic measures, they were also treated variously with sedatives, warmth, alternating suction and pressure, and the oscillating bed. The clinical results were what might have been expected if papaverine had not been added to the therapeutic regimen. One patient (45 years of age) experienced a return of circulation, and the remaining five, all but one of whom were over 50 years of age, developed dry gangrene, necessitating amputation, or died.

COMMENT

This study attempted to determine the efficacy of papaverine as a vasodilator. It has been claimed that papaverine in therapeutic doses can overcome the pronounced reflex vascular spasm which often accompanies acute embolism or thrombosis of a major artery of an extremity. Such cases can rarely be studied under controlled conditions and, as has been noted before, spontaneous recovery frequently occurs without any therapy. We therefore decided to compare under similar conditions the vasodilating qualities of the drug with a simple means of causing arteries to relax, namely, immersion of the opposite pair of extremities in warm water at a temperature of 42° to 46° C. (107.5° to 115° F.). If papaverine could relieve the severe spasm accompanying the acute insult, it should certainly be as effective as warm water is known to be in relaxing lesser degrees of vascular spasm.

Following water immersion vasodilatation was obtained in 11, or 61 per cent, of the eighteen subjects examined (we are omitting the Raynaud syndrome group from statistical comparison). Following the intravenous injection of papaverine hydrochloride only three, or 17 per cent, exhibited any appreciable degree of vasodilatation, as measured by changes in skin temperature and in appearance of the skin. On the other hand, one patient who did not show relaxation of vasomotor tone following water immersion did respond to injections of papaverine hydrochloride.

Any study of the action of drugs on human beings must be interpreted with restraint. In the field of vascular disease, Silbert²¹ has recently expressed a timely reminder that a critical attitude in evaluation of treatment is too often lacking. Nevertheless, we conclude from our observations that as a therapeutic means of causing vascular relaxation in normal individuals or in those suffering from diseases in which vasospasm may play an important role, such as thromboangiitis obliterans and early arteriosclerosis, papaverine hydrochloride intravenously is less effective than immersion of a pair of extremities in warm water. Its efficacy in relieving more severe grades of spasm must therefore be open to question.

SUMMARY

The effectiveness of papaverine hydrochloride intravenously as a vasodilator was studied in a series of eighteen subjects, which included thir-

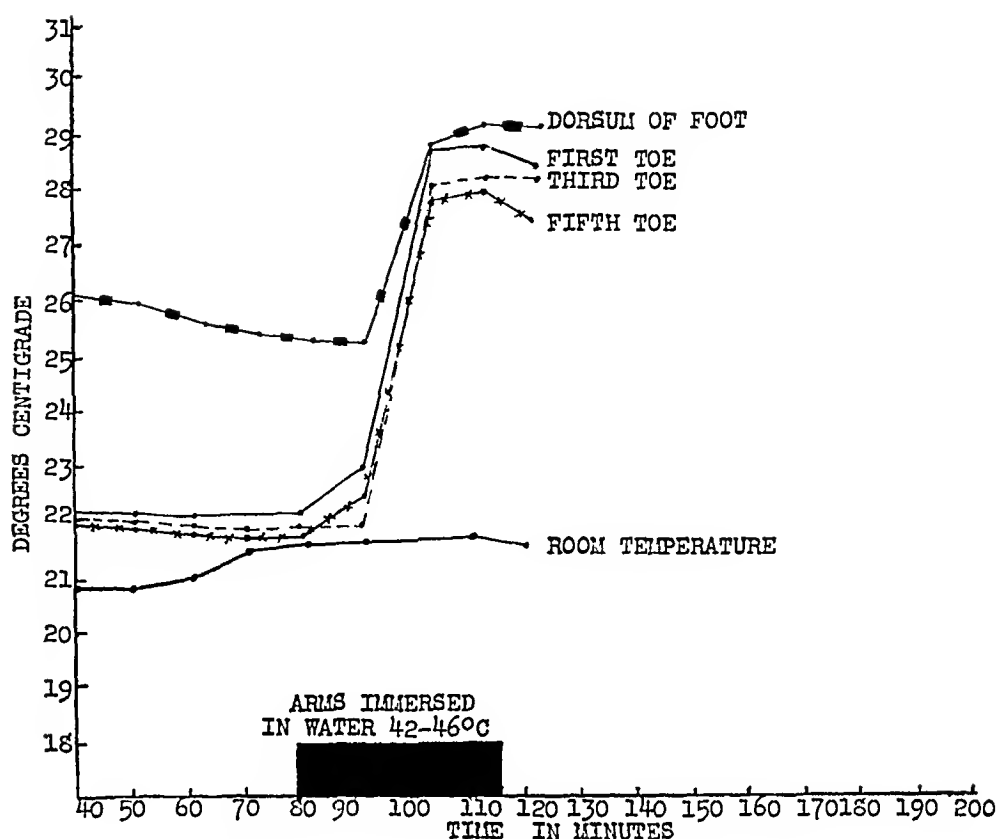


Fig. 14.—Typical experiment showing effect of immersion of arms in water at 42 to 46° C. on the skin temperatures of the toes of the left lower extremity. (Patient G. S., 12/4/37.)

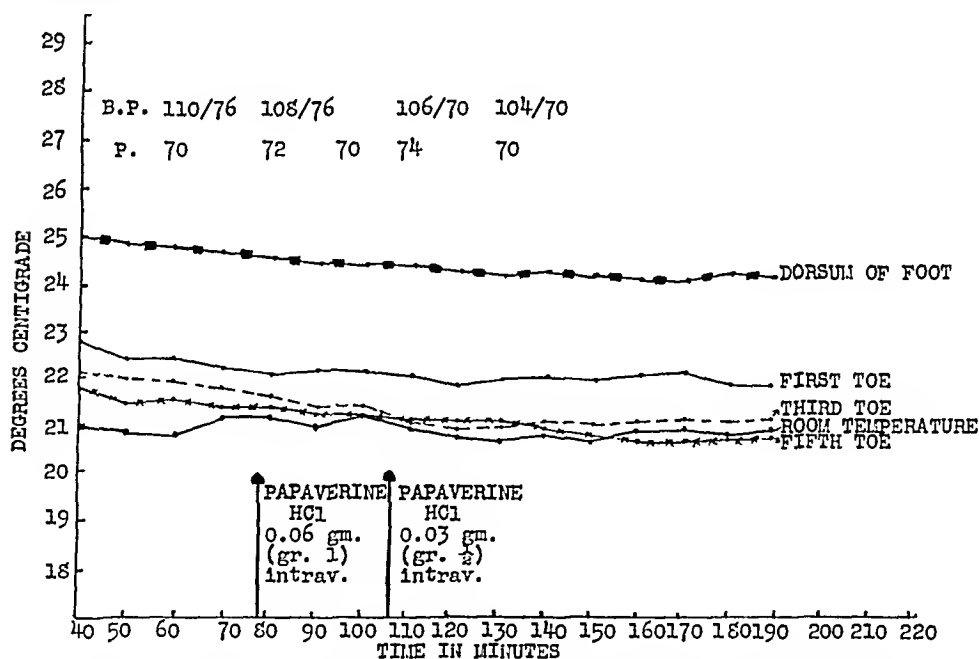


Fig. 1B.—Typical experiment (continued) showing effect of papaverine hydrochloride, administered intravenously, on the skin temperatures of the toes of the left lower extremity. (Patient G. S., 12/9/37.)

TABLE I

COMPARISON OF RESULTS OBTAINED FOLLOWING IMMERSION OF A PAIR OF EXTREMITIES IN WATER AT 42° TO 45° C. AND FOLLOWING INJECTION OF PAPAVERINE HYDROCHLORIDE INTRAVENOUSLY

				PAPAVERINE HYDROCHLORIDE						
CASE NUMBER	SUBJECT	SEX AND AGE	MAXIMAL RISE IN SKIN TEMPERATURE, WATER IMMERSION* (DEGREES C.)	TOTAL INTRAVENOUS DOSE IN ONE HOUR (GM.)	MAXIMAL RISE IN SKIN TEMPERATURE, PAPAVERINE HYDROCHLORIDE*	BLOOD PRESSURE, SYSTOLIC MILLIMETERS MERCURY	PULSE BEATS PER MINUTE	CAPILLARIES	COLOR CHANGES IN EXTREMITIES	SYSTEMIC EFFECTS
<i>Thrombophlebitis Obliterans:</i>										
1.	L. T.	M, 42	No change	0.06	No change	- 8	No change	No change	None	Slightly drowsy
2.	M. S.	M, 41	+8.0	0.06	No change	No change	- 6	No change	None	None
3.	N. B.	M, 41	+8.2	0.06	No change	No change	No change	No change	None	None
4.	A. K.	M, 33	+7.5	0.06	+3.8 C.	-10	- 4	Slightly fuller	Toes pinker	None
5.	A. P.	M, 36	+5.9	0.06	No change	- 6	+ 4	No change	None	None
6.	W. S.	M, 49	+4.0	0.06	No change	+10	+16	No change	None	"Burning beneath heart"
7.	W. Mc.	M, 38	+8.0	0.03	+6.0 C.	-10	-12	Flow faster	Toes pinker	None
8.	E. St. J.	M, 47	No change	0.06	No change	?	?	No change	None	None
9.	J. K.	M, 39	No change	0.06	No change	- 6	-10	No change	None	Throbbing in temples
10.	G. S.	M, 41	+9.0	0.10	No change	- 4	+ 4	No change	None	Momentary dizziness
11.	A. L.	M, 36	No change	0.06	+2.8 C.	- 6	- 6	No change	None	"Flushing in head"
12.	S. F.	M, 43	No change	0.06	No change	- 4	No change	No change	None	Transient drowsiness
13.	H. S.	M, 34	+4.3	0.10	No change	- 6	+ 6	No change	None	Throbbing temples
<i>Arteriosclerosis:</i>										
14.	M. L.	M, 61	No change	0.06	No change	- 8	No change	No change	None	Generalized warmth hours later
15.	J. S.	M, 54	+7.0	0.06	No change	?	- 4	No change	None	None
16.	M. C.	M, 64	No change	0.06	No change	+ 2	- 6	No change	None	Palpitation for 3 minutes
<i>Normal Controls:</i>										
17.	D. L.	M, 31	+9.2	0.10	No change	- 6	- 2	No change	None	Fullness in head 2 minutes, then drowsy
18.	W. H.	M, 40	+6.0	0.06	No change	- 5	No change	No change	None	None

*Average stabilized temperature of skin of toes 20° to 22° C. Rise of less than 2° C. in at least two of the three digits examined in each extremity is considered as no change.

teen who suffered from thromboangiitis obliterans, three who had arteriosclerosis obliterans, and two normals. Four patients with Raynaud's syndrome were also observed, but are not included in the statistical analysis. Compared with the simple water immersion procedure for securing vasodilatation, papaverine hydrochloride is ineffective and uncertain in action.

REFERENCES

1. McGovern, T., McDevitt, E., and Wright, I. S.: Theobromine Sodium Salicylate as a Vasodilator, *J. Clin. Investigation* 15: 11, 1936.
2. Quoted in: Langnecker, H., and Starkenstein, E.: Über die pharmakologische Wirkung einiger neuer Papaverine-Derivativ, *Klin. Wchnschr.* 10: 2257, 1931.
3. Pal, J.: Papaverin und Eupaverin, *Deutsche med. Wchnschr.* 56: 1702, 1930.
4. a. Pal, J.: Über die Papaverinreaktion der glatten Muskeln, ihre diagnostische und therapeutische Verwertung, *Med. Klin.* 9: 1796, 1913.
b. Pal, J.: Das Papaverin als Gefäßmittel und Anestheticum, *Deutsche med. Wchnschr.* 40: 164, 1914.
c. Pal, J.: Experimentelle und klinische Studien über die Wirkung des Papaverins, *Wien. med. Wchnschr.* 63: 1050, 1930.
d. Pal, J.: Über den akut urämischen Anfall und seine Behandlung, *Wien. med. Wchnschr.* 63: 2514, 1913.
e. See reference 3.
f. Pal, J.: Über Perparin: eine papaverinartig wirkende neue Verbindung, *Klin. Wchnschr.* 10: 2261, 1931.
5. Renon, L., and Desbouis, G.: Sur l'action cardiaque experimentale de la Papavérine, *Comp. rend. soc. de Biol.* 76: 526, 1914.
6. Adler, L.: Untersuchungen zur Pharmakologie der Gefäße, *Arch. f. exper. Path. u. Pharmacol.* 91: S1, 1921.
7. Macht, D. I.: A Pharmacologic and Clinical Study of Papaverine, *Arch. Int. Med.* 17: 786, 1916.
8. Barlow, O. W.: Tranquilizing Potency of Morphine, Pantopon, Codeine, Papaverine, and Narcotine, *J. A. M. A.* 99: 986, 1932.
9. Gruber, C. M., and Robinson, P. I.: Studies on the Influence of Morphine, Papaverine, and Quinidine Upon the Heart, *J. Pharmacol. & Exper. Therap.* 37: 429, 1929.
10. Mercier, F.: Sur l'action cardio-vasculaire experimentale de la papaverine, *Comp. rend. soc. de Biol.* 108: 977, 1931; *ibid.* 109: 893, 1932.
11. Gruber, C. M., and Robinson, P. I.: Influence of Morphine, Papaverine, etc., on Intestinal Activity, *J. Pharmacol. & Exper. Therap.* 37: 101, 1929.
12. Gruber, C. M., and Brundage, J. T.: Effects of Papaverine Hydrochloride Upon Non-Anesthetized Dog's Intestine Subjected to Different Pressures, *J. Pharmacol. & Exper. Therap.* 53: 445, 1935.
13. Samaan, K.: Eupaverine: an Experimental Investigation in Relation to Papaverine and Visammin, *Quart. J. Pharm.* 9: 23, 1936.
14. Gross, E. G., and Slaughter, D. H.: The Action of Papaverine on the Muscular Activity of the Alimentary Canal, *J. Pharmacol. & Exper. Therap.* 43: 551, 1931.
15. Samaan, K.: Pharmacological Basis of Drug Treatment (Papaverine, Atropine, and Visammin), *Brit. J. Urol.* 5: 213, 1933.
16. a. Denk, W.: Zur Behandlung der arteriellen Embolie, *München. med. Wchnschr.* 81: 437, 1936.
b. Denk, W.: Weitere Erfahrungen mit der unblutigen Behandlung der Embolie, *Zentralb. f. Chir.* 63: 2, 1936.
17. Allen, E. V., and MacLean, A. R.: Treatment of Sudden Arterial Occlusion With Papaverine Hydrochloride, *Proc. Staff Meet. Mayo Clin.* 10: 216, 1935.
18. De Takats, G.: The Use of Papaverine in Acute Arterial Occlusions, *J. A. M. A.* 106: 1003, 1936.
19. Landis, E. M., and Gibbon, J. H.: A Simple Method of Producing Vasodilatation in the Lower Extremities, *Arch. Int. Med.* 52: 785, 1933.
20. Uprus, V., Gaylor, J. B., and Carmichael, E. A.: Vasodilatation and Vasoconstriction in Response to Warming and Cooling the Body, *Clin. Sc.* 2: 301, 1936.
21. Silbert, S.: Evaluation of Results in Treatment of Peripheral Circulatory Diseases, *AM. HEART J.* 15: 265, 1938.

OBSERVATIONS ON THE GENESIS OF RENAL HYPERTENSION*

L. N. KATZ, M.D., M. FRIEDMAN, M.D., S. RODBARD, B.S., AND
W. WEINSTEIN, M.D.
CHICAGO, ILL.

ALTHOUGH various observers, notably Cash,¹ have noted that hypertension resulted when the kidneys were damaged, it was the fundamental work of Goldblatt, Lynch, Hanzal, and Summerville² which clearly indicated that severe, persistent hypertension may be of renal origin. These latter investigators produced experimental hypertension by partially occluding one or both renal arterics of the dog. Since that time Goldblatt and his associates³⁻⁶ have made many valuable contributions to our knowledge of hypertension of this type. The renal hypertension produced by renal ischemia has been shown by various observers⁶⁻¹¹ to be independent of the nervous system, but the exact mechanism involved is still unknown.

For the past four years we have been interested in the mechanism responsible for the rise of pressure following renal ischemia. In this report we briefly describe our experiences to date.

GENERAL METHOD

Trained dogs were used throughout. In our early experiments the blood pressure was determined by an indirect cuff method, applying the cuff to the upper foreleg. The systolic and diastolic pressures were determined by auscultation over the brachial artery, employing the usual criteria. The cuff was constructed to fit the shape of the limb and was 4 to 8 cm. wide, depending on the size of the animal (modified Ferris and Hynes method¹²). Experienced observers can obtain readings with an error not exceeding ± 5 mm. Hg with trained dogs. However, more accurate blood pressure readings were recorded with the calibrated needlemanometer of Hamilton.¹³ By this method the direct and accurate measurement of both the systolic and diastolic pressure in the femoral artery was obtained. Blood pressures could be recorded without a general anesthetic or morphine, provided care was taken to train the dogs. In general, the training process involved educating dogs to lie quietly for 5 to 10 minutes and making the arterial puncture without applying restraints. The skin overlying the artery was infiltrated with $\frac{1}{2}$ to 2 c.c. of 2 per cent procaine hydrochloride, and sharp needles (20 gauge) were used for the puncture. Often the dogs were so well trained that the arterial puncture could be made without using the local anesthetic. Successive blood pressures were taken at daily to biweekly intervals until three or four successive readings were in agreement within ± 5 mm. Hg. These last readings constituted the control pressure. Occasionally, a marked variation in blood pressure concomitant with various phases of the respiratory cycle was noted, and when this occurred the average systolic and diastolic pressures were calculated. Renal hypertension was produced by completely

*From the Cardiovascular Department, Michael Reese Hospital, Chicago, Ill.
Aided by the A. D. Nast Fund for Cardiac Research.
Received for publication Aug. 16, 1938.

occluding the renal artery with a Goldblatt clamp, then releasing the clamp approximately one-half to one and a quarter turns of the screw. Bilateral clamping in two stages was done 7 to 46 days apart in all but 3 instances. The renal artery constriction was performed under nembutal or ether anesthesia, using the retro-peritoneal approach.

THE ARTERIAL BLOOD PRESSURE OF THE NORMAL TRAINED DOG

We have analyzed our data in order to establish the normal pressures in trained dogs. Blood pressure determinations were made by means of the Hamilton method. The results on 127 trained dogs are shown in Fig. 1. It was found that the mean systolic pressure was 155 mm. Hg, with the range from 130 to 185 and the standard deviation 11 mm. Hg. The mean diastolic pressure was 80 mm. Hg, the range 65 to 100, and the standard deviation 6 mm. Hg (Fig. 2).

The readings in the upper extremity determined in sixteen trained dogs by the cuff method showed a diastolic pressure averaging 85 mm. Hg and ranging from 75 to 100, which is similar to that in the femoral. The systolic pressure, however, was lower, the average being 130 mm. Hg, with 115 to 155 as the range.

TABLE I

NORMAL BLOOD PRESSURE IN THE BRACHIAL ARTERIES OF 16 TRAINED DOGS, OBTAINED BY THE CUFF METHOD

DOG	SYSTOLIC	DIASTOLIC
J-1	130	75
J-2	140	80
J-3	115	75
J-4	155	100
J-6	120	80
J-7	130	100
J-8	145	90
J-9	115	85
J-13	125	85
J-14	140	85
J-16	125	80
J-19	135	90
J-22	125	80
K-9	135	85
K-10	150	95
K-12	130	75

During the initial part of the training period the dogs regularly exhibited hypertension, but usually after 5 to 7 days of daily pressure determinations the basal control level was reached. Occasionally, dogs maintained a high pressure (200/100) with a slow pulse, even after weeks of training. These dogs were discarded. Also discarded were several dogs showing fluctuating pressures, indicating vasomotor instability. A single determination of the blood pressure of untrained dogs, with or without the use of morphine, does not appear to give the correct control blood pressure level.

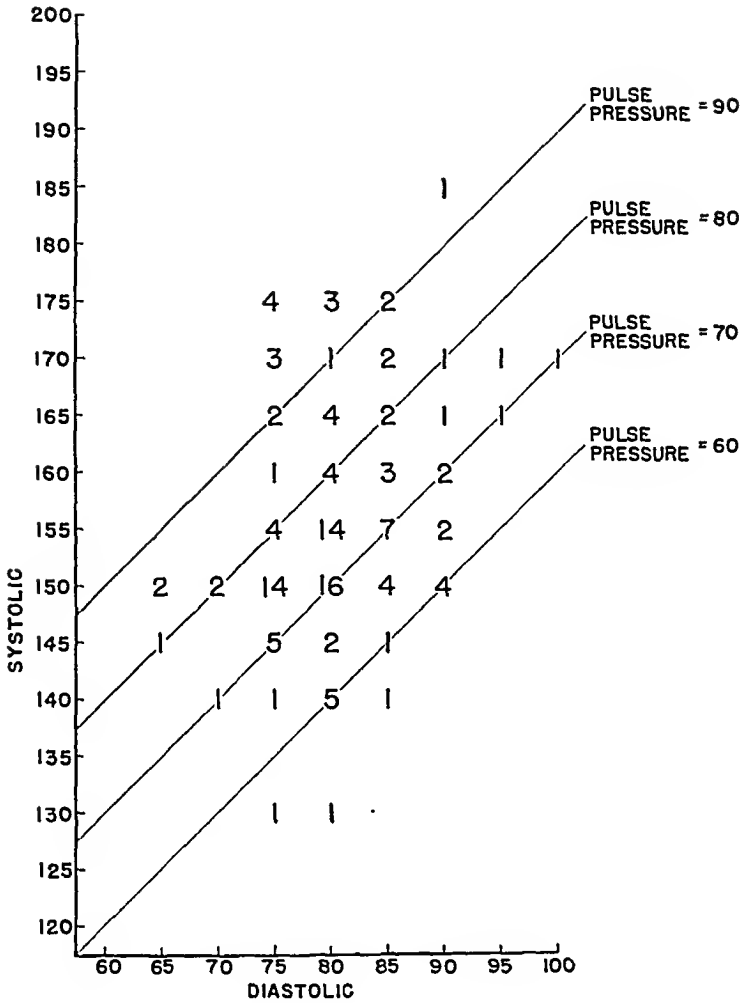


Fig. 1.—The distribution of blood pressures in the femoral arteries of 127 trained normal dogs, obtained by direct intra-arterial puncture (of Hamilton). The systolic pressure is given in ordinates and the diastolic pressure in abscissae. The pulse pressure is indicated by the oblique lines. All pressures are in millimeters of mercury. The figures give the number of animals with each particular combination of systolic, diastolic, and pulse pressures.

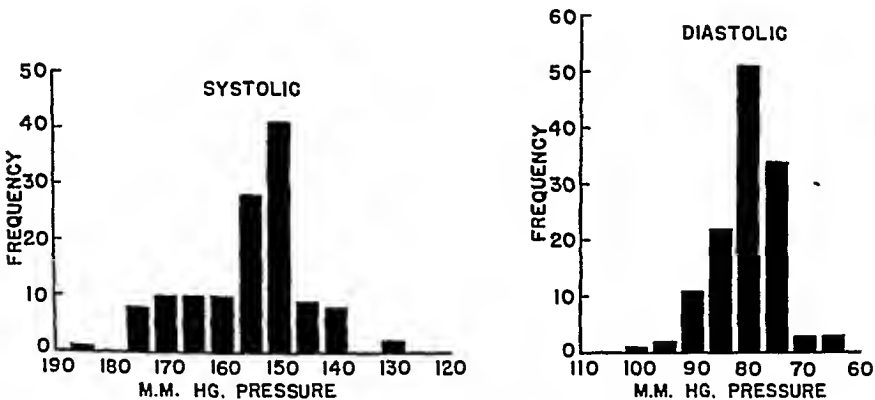


Fig. 2.—Distribution of pressure values in 127 normal trained dogs.

THE CHANGE IN BLOOD PRESSURE FOLLOWING PARTIAL OCCLUSION OF
ONE RENAL ARTERY

Thirty dogs were used in this phase of the study. The blood pressures were determined by the cuff method in 12, and by direct arterial puncture in 18. A rise in both systolic and diastolic pressure occurred in 80 per cent of the cases, reaching values as high as 225/150, thus indicating a maximum rise of as much as 80/65 mm. Hg. In these 30 dogs the mean rise in pressure was 32/24 mm. Hg. The hypertension lasted from 2 to at least 46 days after the single clamp was applied. In this last animal the hypertension was not permitted to run its full course. Other observers^{2, 5} have found sustained rises for longer periods in some of their dogs. None of the 14 animals in which blood nonprotein nitrogen determinations were made showed an abnormal nonprotein nitrogen level, and none developed uremia.

This variability in the duration of hypertension is not completely dependent upon the degree of occlusion alone, but in part on the functional integrity of the other kidney. Favoring this concept are observations^{10, 14} on dogs with unilaterally clamped renal arteries in which the removal of the normal kidney leads either to a greater elevation of the blood pressure or to the restoration of hypertension. This indicates clearly that the normal kidney in some manner compensates for the deleterious effects of the ischemia in the other kidney. Whether the normal kidney merely acts as a partial or complete substitute for some missing function of the ischemic kidney, or acts to neutralize, destroy, or excrete the humoral mediator of hypertension which the ischemic kidney produces remains to be determined. However, we feel that the re-establishment of hypertension by removing the normal kidney from an animal whose other kidney is ischemic is an important clue to the possible solution of the mechanism of renal hypertension.

In contrast to the foregoing group of 30 dogs, in 10 dogs a clamp was applied to the renal artery of the remaining kidney from 16 to 91 days following unilateral nephrectomy. The pressure in all these dogs was measured by the direct arterial puncture method of Hamilton. Hypertension occurred in 90 per cent. The maximum level attained was 250/150 mm. Hg, with a maximum rise of 95/80 and an average rise of 58/40 mm. Hg. Five of these 10 animals (all 5 had hypertension) died in uremia, 3, 3, 4, 7, and 17 days, respectively, after the renal artery was clamped. Three of the remaining five dogs failed to develop uremia, although 2 of these had hypertension. The duration of hypertension in those animals not dying in uremia was found to continue for an indefinite period, up to at least 10 months. At necropsy, one of the dogs dying in uremia with hypertension showed extensive petechiae in its viscera, exclusive of the kidney, confirming the recent report of Goldblatt¹⁵ concerning the pathologic changes following severe hyper-

TABLE II
EFFECT OF RENAL ARTERY CLAMPING ON BLOOD PRESSURE

	NO. OF DOGS IN SERIES	MEAN PRESSURE RISE	MAXIMUM PRESSURE RISE	NO. OF DOGS SHOWING HYPERTENSION	NO. OF DOGS SHOWING RISE IN NPN OF BLOOD	NO. OF DOGS DYING OF UREMIA	RANGE OF DURATION OF HYPERTENSION PERIOD
Unilateral renal artery clamp only	30	32/24	80/65	23 out of 30 measured	0 out of 14 measured	0 out of 30	2 to at least 46 days
Unilateral nephrectomy followed by renal ar- tery clamp	10	58/40	95/80	7 out of 8 measured	5 out of 8 measured	5 out of 10	110 to at least 302 days
Bilateral renal artery clamp	24	54/40	95/85	21 out of 23 measured	11 out of 18 measured	7 out of 24	31 to at least 420 days

tension with renal insufficiency. A second dog showed fibrinous pericarditis. The absence of the second kidney is thus seen to facilitate the production of hypertension and prolong its course, although frequently leading to uremia.

THE CHANGE IN ARTERIAL BLOOD PRESSURE FOLLOWING PARTIAL OCCLUSION OF BOTH RENAL ARTERIES

Bilateral partial renal arterial occlusion was produced in 24 dogs. The occlusion was done in one stage in 3, and in two stages in the other 21 dogs, 7 to 46 days apart. In 10, the pressure was measured by the cuff method and, in the remaining 14, by the direct arterial puncture method of Hamilton. The effects were more severe than those following the production of renal ischemia in but one of two kidneys; they were similar to those following partial renal occlusion after unilateral nephrectomy. Thus, hypertension occurred in 85 per cent of the animals, and lasted, with 1 exception, as long as the animal lived, viz., 2 days to 14 months. In this one instance the animal died in uremia and, 7 days before death, the pressure fell to normal as the uremia developed. The highest pressure level attained in these 24 dogs was 245/150, representing a maximum rise of 95/70 mm. Hg. The average rise was 54/40 mm. Hg. Seven of these animals (28 per cent) died in uremia, 2, 2, 3, 4, 5, 30, and 38 days, respectively, after the second clamp was applied. Elevation of the nonprotein nitrogen of the blood was noted in 11 of the 18 animals.

One of the animals with simultaneously produced bilateral renal arterial clamping is worth discussing in this connection. This animal, T 29, showed no elevation of blood pressure or nitrogen retention for 19 days following the bilateral clamping. Following unilateral nephrectomy, the nonprotein nitrogen rose from 45 to 108 mg. per cent without a concomitant elevation of blood pressure. The animal was in excellent condition, although the nonprotein nitrogen elevation persisted for 20 days, at which time the animal was sacrificed. This phenomenon of renal excretory insufficiency in a unilaterally nephrectomized animal whose other renal artery has been clamped, without an accompanying hypertension, we have seen once before,¹⁴ but have not seen described elsewhere. It suggests that the cause of the occasional failure of hypertension to develop following partial renal arterial occlusion is not always an inadequate degree of occlusion, but must be sought for elsewhere. It also indicates that hypertension and renal excretory insufficiency are not necessarily related.

THE EFFECT OF VARIOUS PROCEDURES ON RENAL HYPERTENSION

During the course of this study an epidemic of distemper occurred among the dogs. It was observed that distemper often (4 out of the

6 dogs who survived) caused a significant lowering of the blood pressure with a return to hypertensive levels on convalescence. This was not due to the concomitant starvation or dehydration, since neither of these conditions had any influence on the hypertension of 2 dogs in which their effect was tested. The most likely explanation of the fall in blood pressure in distemper-infected dogs would seem to lie in a partial peripheral vasomotor collapse.

In view of the results obtained by Goldblatt⁵ following adrenalectomy, and those obtained by Page¹⁶ following extirpation of the pituitary in renal-hypertensive dogs, we tested the effect of subtotal thyroparathyroidectomy in 3 hypertensive dogs. In these animals the deleterious effects of parathyroidectomy were counteracted satisfactorily with calcium citrate in the food, calcium chloride by vein, and parathormone by subcutaneous injection. It was found, in accord with Glenn and Lasher,¹⁷ that the removal of most of the thyroid does not influence the blood pressure in the renal-hypertensive dog. However, it must be emphasized that the removal of both thyroid lobes in the dog does not produce a myxedematous state, because of the abundance of accessory thyroid tissue.

THE GROSS AND HISTOLOGIC APPEARANCE OF THE ISCHEMIC KIDNEY

On gross inspection, the ischemic kidney usually showed no abnormality. In animals with one ischemic kidney, the ischemic kidney usually appeared smaller than the normal one. Histologic sections of 8 ischemic kidneys were examined, and the glomeruli, tubules, arterioles, and interstitial tissue were studied. Dr. M. Corrigan, of the department of pathology, checked these sections with one of us (M. F.). The striking finding, as Table III shows, is the absence of definite abnormalities. Only in 2 kidneys were occasional arterioles found that were

TABLE III
HISTOLOGIC APPEARANCE OF ISCHEMIC KIDNEYS

DOG NUMBER	DURATION OF ISCHEMIA	GLOMERULI	TUBULES	INTERSTITIAL TISSUE	ARTERIOLES
K-A	12 days	Occasional hyalinization	Normal	Normal	Abnormal
K-B	1 month	Normal	Normal	Normal	Normal
J-4	2 months	Occasional hyalinization	Normal	Normal	Abnormal
K-4A	5 months	Normal	Normal	Normal	Normal
K-4B	4 months	Normal	Normal	Normal	Normal
T-2	4 months	Normal	Normal	Normal	Normal
T-1	6 months	Normal	Normal	Normal	Normal
T-R	6 months	Normal	Normal	Normal	Normal

thickened, but this was not a diffuse process, and in one of these kidneys the ischemia was produced but 12 days previously. Similar scattered arteriolar thickening occurred in some of our supposedly normal control kidneys.

Goldblatt and his associates² observed significant changes affecting the glomeruli and arterioles in 3 of their dogs with renal artery clamps. Child¹⁸ also reported definite changes in the glomeruli, arterioles, and tubules of ischemic kidneys, but states that these changes were not present in mildly hypertensive animals, or in those animals which had not had renal ischemia for at least 3 months. Elaut,¹⁹ however, in a similar study, found no changes in ischemic kidneys even after 18 months. Our results are based on a study of kidneys that were rendered ischemic less than 6 months earlier.

THE POSSIBLE EXISTENCE IN THE BLOOD STREAM OF THE HUMORAL MEDIATOR OF RENAL HYPERTENSION

A. Gross Transfusion of Blood Between Unanesthetized Renal-Hypertensive Dog and Unanesthetized Nonhypertensive, Bilaterally Nephrectomized Dog.—Attempts to demonstrate the presence of a humoral mediator with pressor properties in the blood stream of a dog with renal hypertension have been unsuccessful.^{20, 21, 22, 23} Preliminary experiments in which we injected blood taken from renal-hypertensive dogs into normal dogs also failed to show any rise in blood pressure. In view of the experiments described in the preceding sections of this report, the possibility suggested itself that the lack of response might be due to the action of the normal kidneys in the recipient dog. Consequently, we planned to repeat the transfusions of blood from renal-hypertensive animals into nonhypertensive, bilaterally nephrectomized dogs.

The experiments were planned to circumvent, as far as was feasible, the following possibilities: (a) that the humoral mediator might be present in extremely small concentrations, (b) that the presence of normal kidneys might clear even this small quantity of the humoral mediator, (c) that the humoral mediator might require hours to manifest its vasopressor action, (d) that anesthesia might mask this effect, and (e) that in a dog without kidneys certain changes in its blood might occur which would have a vasodepressor action or in some other fashion prevent the action of the chemical mediator.

Trained normal dogs whose blood matched that of the hypertensive animal were used in the experiment. Beginning a few hours after bilateral nephrectomy, after the dogs had recovered from the effects of the ether anesthesia, they were cross-transfused every 2 to 3 hours with renal-hypertensive dogs. Blood was drawn into 100 c.c. syringes, previously rinsed in $\frac{1}{2}$ per cent citrate solution, from the femoral artery of the hypertensive dog and transferred immediately in 100 c.c. quantities into the brachial vein of the bilaterally nephrectomized animal. After 200 to 300 c.c. were transferred, the procedure was immediately reversed, the nephrectomized dog now acting as the donor. This was repeated many times. Thus the hypertensive dog received blood from the

TABLE IV
THE EFFECT OF HYPERTENSIVE BLOOD ON THE NONHYPERTENSIVE BILATERALLY NEPHRECTOMIZED DOG

	BLOOD PRESSURE LEVEL BEFORE NEPHREC- TOMY MM. HG	BLOOD PRESSURE AFTER NEPHREC- TOMY BEFORE THE TRANS- FUSION MM. HG	INTERVAL BETWEEN NEPHREC- TOMY AND START OF TRANS- FUSION HOURS	DURATION OF TRANS- FUSION PERIOD HOURS	AMOUNT OF BLOOD TRANS- FUSED C.C.	EFFECT OF TRANS- FUSION	DONOR DOG
(1) T-3	160/85	-	16	8	785	No rise. Prolonged late gradual fall.	Hypertension 102 days' dura- tion (single ischemic kidney)
(2) T-6	150/85	190/100	2	22	1785	Initial rise (10 mm.) followed later by a gradual fall.	a) Hypertension 30 days' dura- tion (single ischemic kidney) b) Hypertension 32 days' dura- tion (single ischemic kidney —other kidney normal)
(3) T-25	155/80	180/100	2	20	2400	No rise. Prolonged late gradual fall.	Hypertension 38 days' duration (single ischemic kidney)
(4) T-53	160/80	175/100	6	15	1510	No rise. Prolonged late gradual fall.	Hypertension 49 days' duration (both kidneys ischemic)

nephrectomized dog to clear of uremic products, and the nephrectomized dog received hypertensive blood. Blood pressure determinations were made 1 hour after each cross-transfusion. A summary of the details of the four experiments of this type is given in Table IV, and typical changes in one of the bilaterally nephrectomized dogs are shown in Fig. 3. The hypertensive dogs used as donors had an elevated blood pressure of 30 to 102 days' duration previous to the transfusion. From 785 to 2400 c.c. of blood were cross-transfused during each experiment.

It will be seen that despite all of these measures there was no rise in blood pressure in any of the nephrectomized dogs. It will be noted, however, that in the 3 dogs in which the blood pressure changes in the first few hours following the bilateral nephrectomy were measured a definite rise in pressure occurred, which is attributable to the nephrectomy itself.

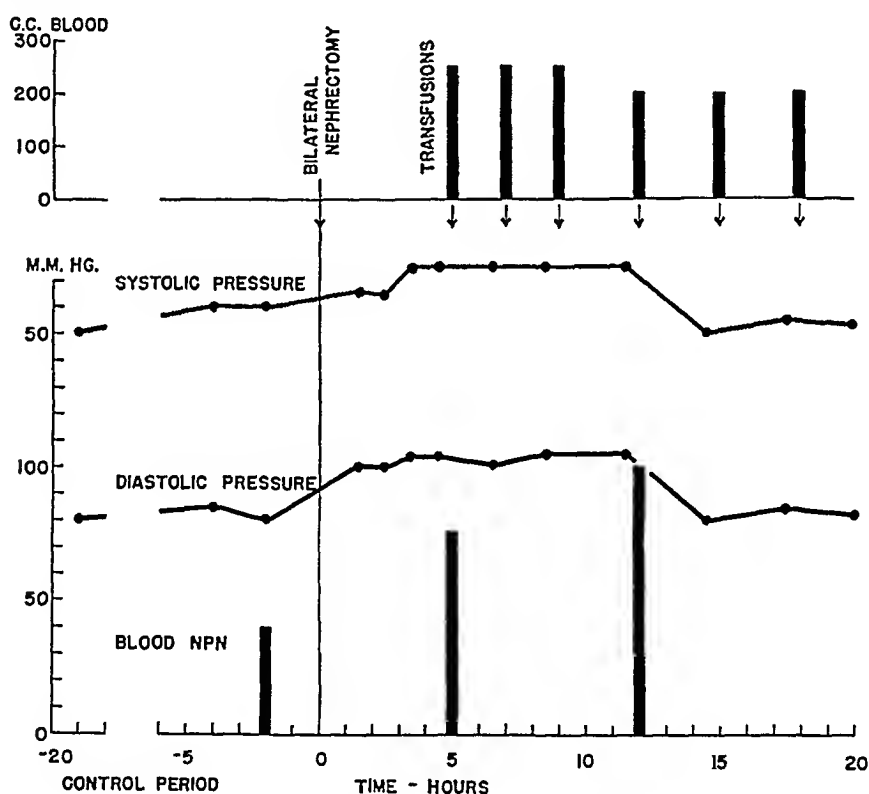


Fig. 3.—Typical cross-transfusion experiment showing effect on bilaterally nephrectomized recipient dog.

The absence of any evidence of vasopressor action of renal-hypertensive blood in these long-continued cross-transfusions with unanesthetized nephrectomized dogs indicated that if a pressor substance is in the blood it must be present in extremely minute quantities or be extremely labile. The negative results cannot be attributed to a lack of time for the development of the rise in pressure, since our experiments continued much

longer than the time necessary for the blood pressure rise to occur after bilateral complete ligation of the renal arteries.

The blood pressure curve in the bilaterally nephrectomized dogs receiving hypertensive blood was identical to that of a bilaterally nephrectomized dog receiving normal blood. In short, the direct proof that there is a humoral mediator in the blood of renal-hypertensive dogs which acts to produce an elevation of pressure remains to be adduced.

B. Hind-Leg Perfusion Experiments.—Equally negative results were obtained when a hypertensive animal was used as the donor in perfusing the hind leg of another dog. This procedure was used to determine whether or not the failure to obtain a pressor response in the cross-transfusion experiments might have been due to the slow rate of transfer of blood relative to the mass of tissue upon which it was to act.

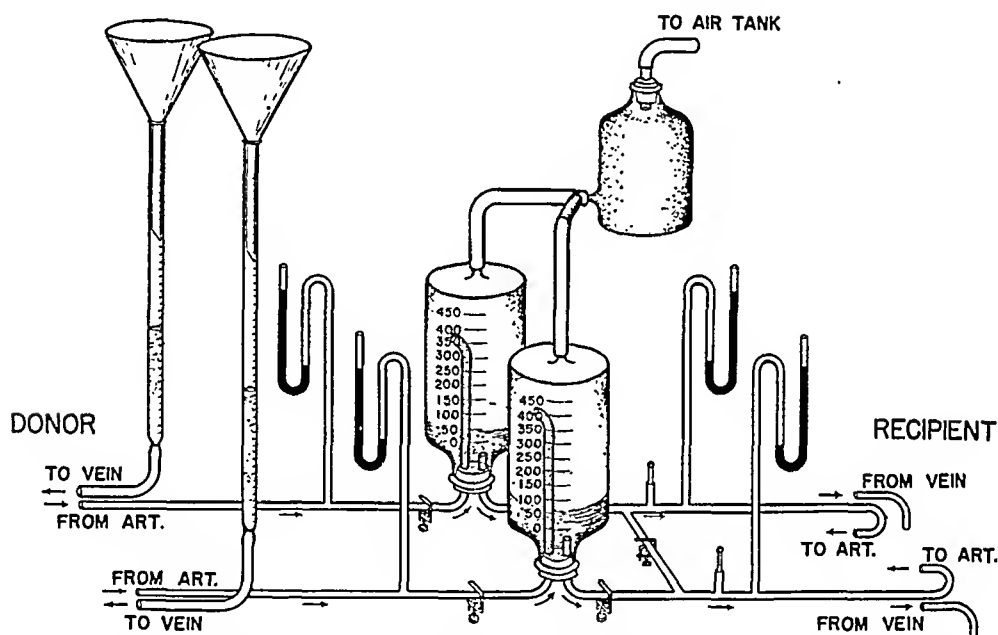


Fig. 4.—The perfusion apparatus consists of a pair of control pressure bottles of 500 c.c. capacity partially filled with blood and maintained at a constant level. These bottles are connected through an air trap with a large compressed air tank at a pressure of 60 mm. Hg. The blood temperature is maintained at 35° C. The blood from the bottles is permitted to flow into the femoral artery of the isolated recipient limb. A very tight cutting tourniquet is applied to the limb above the cannulae. The dog is then bled to death and his blood is used as a reserve. The rate of blood flow from the isolated limb is measured at the femoral vein in a graduated cylinder and returned manually and continuously to the burettes connected to the femoral veins of the donor dog. The rate of inflow into the donor dog is adjusted to keep pace with the rate of blood outflow via the femoral arteries in order to maintain a constant blood level. The adjustment of femoral vein inflow and femoral artery outflow of the donor dog is made by screw clamps. Discussed in text.

A method for measuring the vasomotor changes under constant temperature and pressure in the isolated, denervated limb, as given by the outflow from the leg vein, is depicted in Fig. 4.

In the first experiment (Fig. 5) we demonstrated that the perfusion of the isolated limb with blood from a nonhypertensive donor could be maintained constant within small limits over a long period, in this case

two and one-half hours. The blood vessels of this preparation at the end of this time were still responsive to the vasoconstrictor action of adrenalin.

In this experiment, both donor and recipient were anesthetized with nembutal (25 mg. per kg.). We used the new purified heparin, recently developed by Scott and Charles,²⁴ in quantities sufficient to maintain the blood noneoagulable. A surplus pool of heparinized blood was obtained from a third dog to keep the perfusion system filled without diminishing the blood volume of the donor dog. Preliminary experiments showed that this procedure was essential to avoid shock.

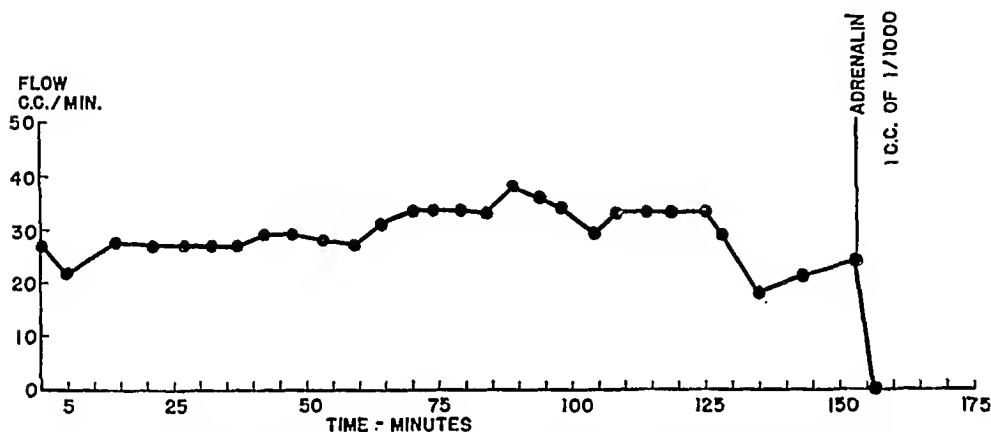


Fig. 5.—Effect of protracted perfusion of nonhypertensive heparinized blood on flow in isolated denervated hind-limb preparation (nembutal anesthesia).

The maintenance of a constant flow when the pressure head was constant and a response to adrenalin by the vascular system in this preparation at the end of 2½ hours encouraged us to repeat the experiment with a hypertensive donor. The procedure was modified from that used in the preceding experiment. A hypertensive donor dog was prepared, as well as the nonhypertensive. Only one femoral artery and vein of each donor was cannulated, and both hind limbs of the recipient (about 8 kg. in weight) were prepared (Fig. 6). One inflow bottle was connected to the artery of the nonhypertensive dog and the other to the artery of the hypertensive dog.* At the start, both hind legs were perfused with blood from the nonhypertensive dog. After 20 minutes, the right hind limb was perfused with 4100 c.c. of blood from the hypertensive dog in the next 100 minutes. While a slight slowing of flow occurred, it was no greater than the reduction of flow in this same period in the left hind leg, in which “nonhypertensive” blood was used. Furthermore, the vessels of the perfused hind limb were shown to be responsive to adrenalin at the end of the experiment.

*The hypertensive dog, T-32, had had renal hypertension for 65 days.

The possibility existed that the absence of a vasopressor action by the hypertensive blood was due to the depression by nembutal of the vasomotor response—an action recognized in barbiturate anesthetics. The experiment was, therefore, repeated, using chloralosan as the anesthetic. According to Heymans (personal communication), chloralosan has little or no effect on vasomotor responses. In the experiment shown in

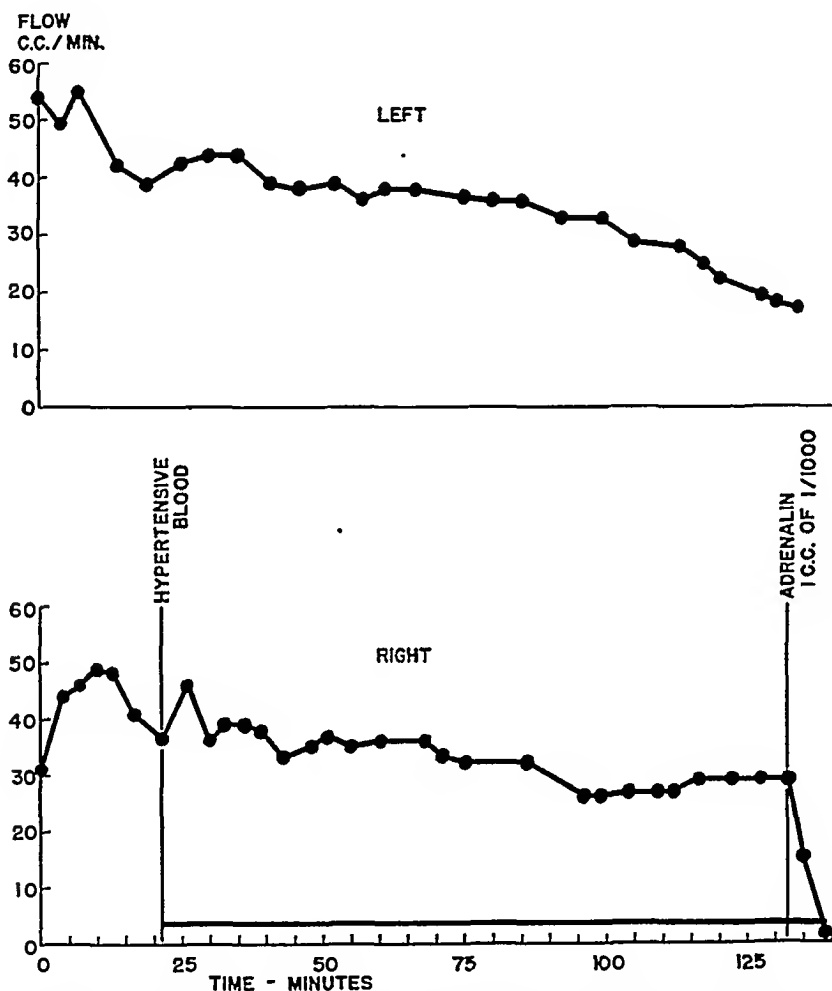


Fig. 6.—Effect on blood flow of hypertensive and nonhypertensive heparinized blood. In right, isolated, denervated, hind-limb preparation. Horizontal line below curve indicates period of perfusion with hypertensive blood. In the left, isolated, denervated, hind-limb preparation, nonhypertensive heparinized blood was perfused as a control.

Fig. 7, therefore, the same procedure was used as in the preceding experiment except that chloralosan (95 mg. per kg.) was used as the anesthetic in all of the dogs—recipient, bleeder, normal, and hypertensive donors. In this experiment we found that the hypertensive blood caused an immediate vasodilatation when substituted for the nonhypertensive blood on three occasions, twice in the right and once in the left leg. In all three instances the substitution of nonhypertensive blood returned the flow at once to its previous level. The vasodilatation decreased progressively as perfusion of the hypertensive blood was con-

tinued, apparently because of a local compensatory mechanism which persisted for a brief period after the perfusate was changed back to nonhypertensive blood. Two thousand five hundred e.e. of hypertensive blood were perfused into the right leg and 500 e.e. into the left leg within 50 and 15 minutes, respectively.*

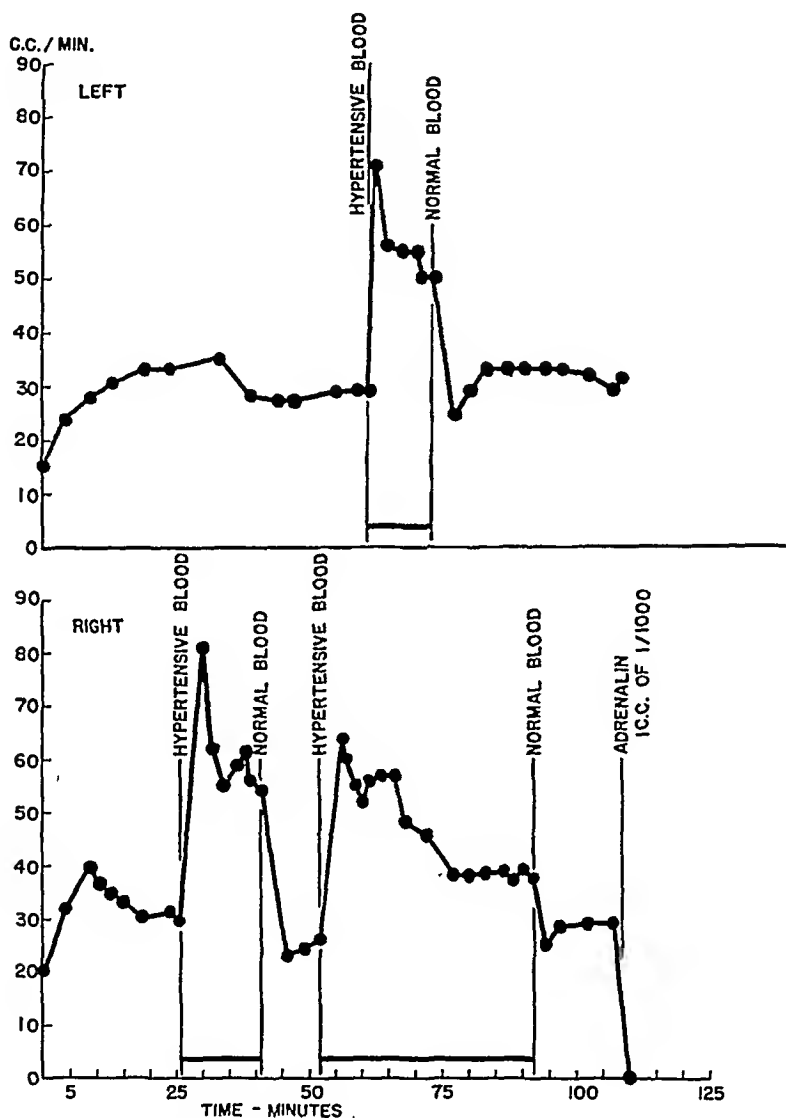


Fig. 7.—Effect on blood flow of hypertensive and nonhypertensive heparinized blood in right and left isolated hind-leg preparations, the horizontal line below flow curves indicates periods of perfusion with hypertensive blood.

The fact that a vasopressor action was absent in two experiments, and that a vasodilator action was present in one, is in accord with work of Prinzmetal, et al.²⁰ It indicates that various anesthetics may alter vasomotor response, or that the vasoconstriction responsible for the renal

*The renal hypertension in the hypertensive donor dog, T-56, was of 7 days' duration.

hypertension is in some other vascular bed than that of the extremity, or that the response occurs only when the leg is innervated or, most likely, that the amount of humoral mediator present in the blood stream is too small or too labile to exhibit its action in such perfusion experiments. At all events, we have failed to demonstrate directly the presence of a humoral mediator in the blood of dogs with renal hypertension.

RELATION OF BILATERAL NEPHRECTOMY AND BILATERAL RENAL ARTERY LIGATION TO HYPERTENSION

We observed in the cross-transfusion experiments that bilateral nephrectomy led to an immediate rise in blood pressure in normal dogs, a phenomenon not mentioned elsewhere, to our knowledge. In order to elucidate the mechanism of this pressure rise, 7 more dogs were subjected to bilateral nephrectomy. Three other dogs were subjected to a mock operation resembling the double nephrectomy in all details except only that the kidneys were not removed. For comparison, 2 dogs were subjected to complete bilateral renal arterial ligation. All of these operations were done under ether anesthesia and none of the animals in this series showed any evidence of discomfort after the operation. Blood pressures were measured frequently, beginning 1 hour after operation.

TABLE V

EFFECT OF BILATERAL NEPHRECTOMY AND BILATERAL RENAL ARTERY LIGATION ON BLOOD PRESSURE

DOG	CONTROL BLOOD PRES- SURE BEFORE OPERATION MM. HG	MAXIMUM BLOOD PRES- SURE LEVEL AFTER OPERATION MM. HG	MAXIMUM RISE IN BLOOD PRES- SURE FOL- LOWING OPERATION MM. HG	TIME LAG BEFORE BLOOD PRES- SURE RISE OCCURRED HOURS	DURATION OF BLOOD PRES- SURE ELEVATION HOURS	BLOOD PRES- SURE 15 HOURS AFTER OPERATION MM. HG
<i>Bilateral Nephrectomy</i>						
K 42*	190/100	225/130	35/30	1	6½	215/105
T 38	150/ 85	185/100	35/15	1	4½	155/ 85
T 40	195/100	215/110	20/10	1	6½	190/ 90
T 42	165/ 85	210/125	45/40	1	11	150/ 90
T 48	145/ 80	155/100	10/20	1	2½	95/ 60
T 74	150/ 80	180/105	30/25	1	6	150/ 70
T 75	150/ 75	150/110	0/35	1	6	Dead
<i>Complete Bilateral Renal Artery Occlusion</i>						
T 4	175/ 95	220/140	45/45	10	48	220/130
T 5	140/ 70	205/125	65/55	1	48	180/120
<i>Control Mock Operation</i>						
K 63	165/ 90	185/110	20/20	1	5	150/ 95
T 29	175/ 80	185/ 85				185/ 85
T 45	170/ 80	175/ 80				145/ 80

*This dog had renal hypertension at time of nephrectomy.

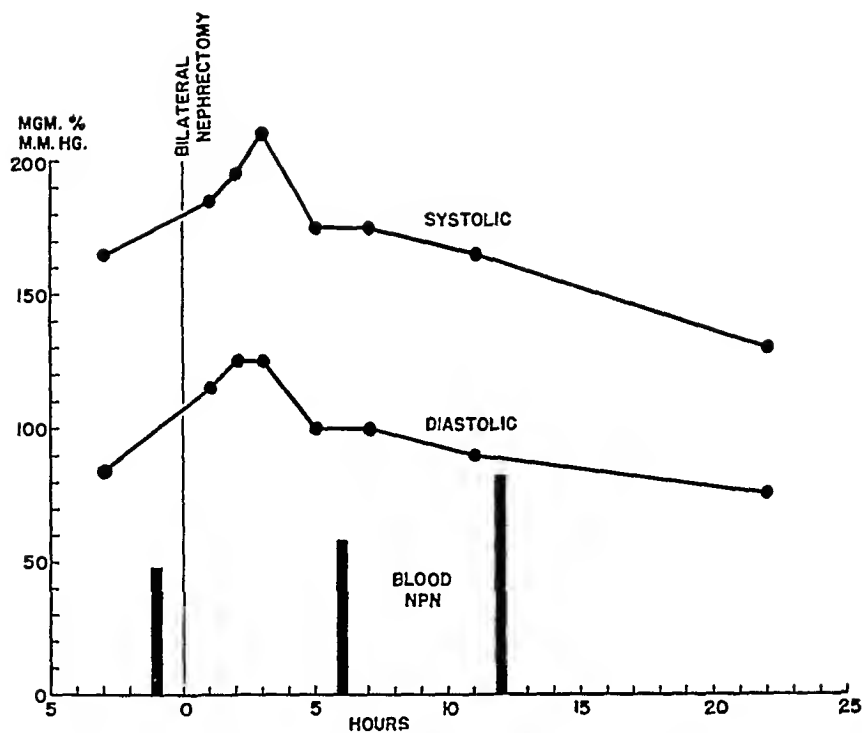


Fig. 8.—Typical effect of bilateral nephrectomy on blood pressure and blood non-protein nitrogen.

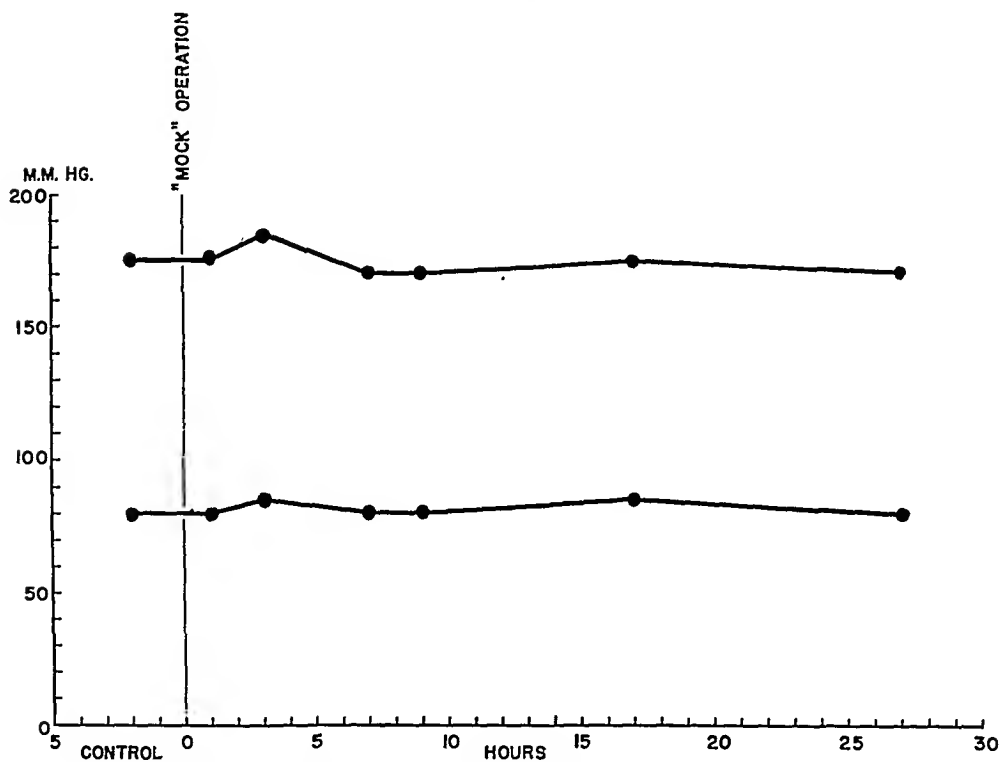


Fig. 9.—Typical effect of mock operation on blood pressure.

The results are summarized in Table V and in typical curves shown in Figs. 7, 8, and 9. It will be seen that the mock operation had no significant effect on the blood pressure, whereas bilateral nephrectomy caused a temporary rise of as much as 45/40 mm. Hg, lasting up to 11 hours. Further, this rise occurred even in an animal, K-42, with renal hypertension. The rise was not as great nor as persistent as that following complete bilateral renal arterial occlusion.

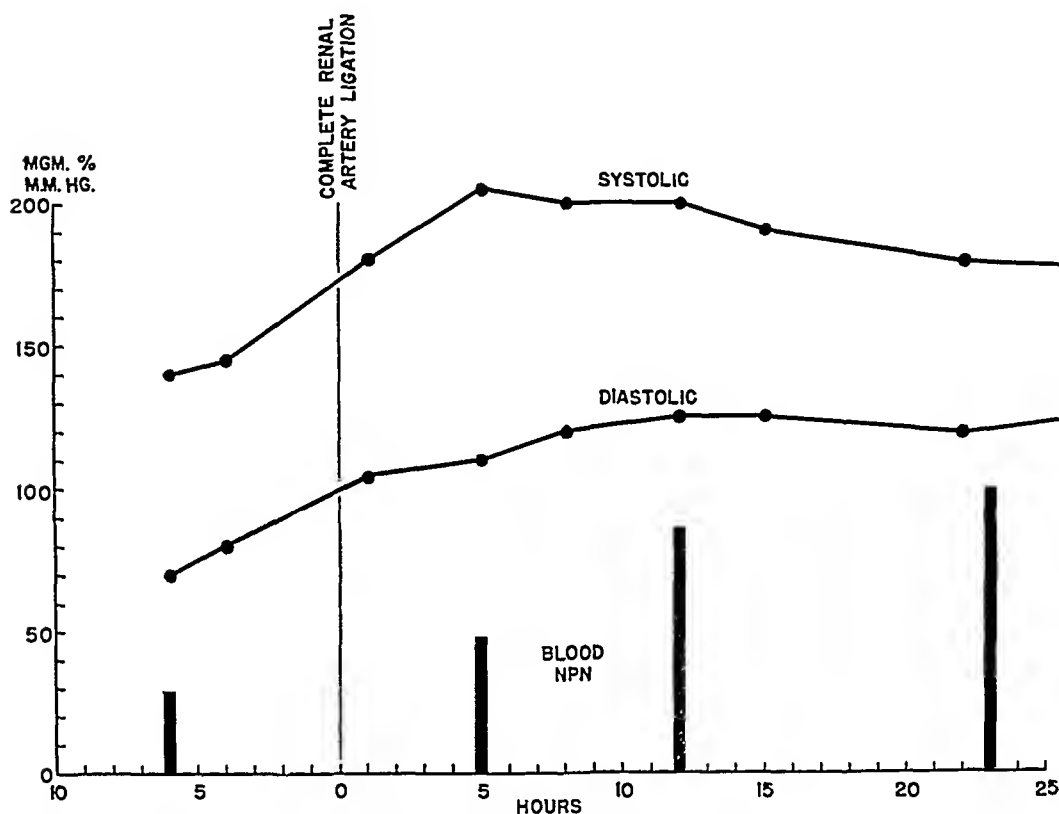


Fig. 10.—Effect of complete bilateral renal arterial ligation on blood pressure and blood nonprotein nitrogen.

The possibility that the transitory hypertension following bilateral nephrectomy was due to the action of retained pressor substances normally excreted or neutralized by the kidneys was dismissed when we found that unilateral nephrectomy in 3 of 4 instances caused a similar temporary rise in blood pressure. The results are shown in Table VI. Therefore, the most likely cause of the temporary hypertension is irritation of afferent pressor nerves located in the neighboring rich nerve plexus. This reflex pressor response is probably unrelated to painful stimulation since repetition of the nephrectomy experiments on 5 dogs under the influence of morphine sulfate gave a similar temporary hypertension.

TABLE VI
EFFECT OF UNILATERAL NEPHRECTOMY ON BLOOD PRESSURE

DOG	CONTROL BLOOD PRES- SURE BEFORE OPERATION MM. HG	MAXIMUM BLOOD PRES- SURE LEVEL AFTER OPERATION MM. HG	MAXIMUM RISE IN BLOOD PRES- SURE FOLLOWING OPERATION MM. HG	TIME LAG BEFORE BLOOD PRES- SURE RISE OCCURRED HOURS	DURATION OF BLOOD PRES- SURE ELEVATION HOURS	BLOOD PRES- SURE 15 HOURS AFTER OPERATION MM. HG
<i>Other Kidney Remaining</i>						
T 66	175/90	225/120	50/30	1	7	
T 68	175/75	175/ 75				
T 71	150/75	175/100	25/25	1	5½	
T 72	140/75	175/105	35/30	1	6½	
<i>No Kidney Remaining</i>						
K 47	160/75	160/ 75				165/80
K 49	180/95	200/ 90				200/90
T 29	170/85	170/ 90				140/70
T 68	175/75	200/ 80				160/65
T 72	125/65	160/ 85	35/20	2½	6½	120/60

DISCUSSION

*The Importance of the Training Period and the Method of Recording
Blood Pressure in Hypertension Studies*

We feel that some of the discrepancies in early work in this field were due to the use of general anesthesia or of untrained dogs when anesthesia was not employed. These facts should be considered in evaluating contradictions. Our experience has convinced us that indirect blood pressure methods do not compare in accuracy with the direct method. We have, therefore, discarded the cuff method and are using the calibrated needle-manometer of Hamilton.

Very few studies have been reported in which the Hamilton manometer was used. Usually, the van Leersum carotid-loop method, giving only the systolic pressure, or femoral arterial puncture with a mercury manometer recording mean pressure, has been employed. In either case exaggeration of the pressure changes is likely to occur. Further, these methods fail to give any indication of the more important criterion of arterial hypertension—the diastolic pressure. The Erlanger-Koll-Cash sphygmomanometer may be used to measure both systolic and diastolic pressure indirectly, but, as pointed by Wood and Cash,²⁵ it is technically difficult. In short, in a field as full of variables as is that of experimental hypertension, it is advisable to utilize the most accurate method of blood pressure recording, the Hamilton manometer, in adequately trained dogs. Standardization of techniques used for the study will lead to comparable results and fewer apparent contradictions.

The Blood Pressure after Nephrectomy

Certain acute experiments in the field of hypertension require the use of nephrectomized animals. In the past, the consensus has been that nephrectomy causes a drop in blood pressure,⁵ although Harrison, et al.,²⁶ have reported a rise in 2 of their 12 dogs on the second and third postoperative days. In our experience, the pressure usually fell by the third day as the animal developed uremia. We know of no other reports of blood pressure changes in the first 20 hours after nephrectomy. In our cross-transfusion experiments we noticed a rise in pressure within an hour or two after nephrectomy. Had we not taken the pressures at this time, we might have been led to ascribe the elevation to the transfusions of hypertensive blood into the nephrectomized dog. This early pressure rise following nephrectomy might have complicated the results of the experiments of Houssay and Fasciolo,¹¹ in which normal and ischemic kidneys were transplanted into the necks of dogs. It is also possible that the initial elevation of pressure following transplantation of the kidneys, as carried out by Blalock and Levy,¹⁰ might have been due to the removal of the kidney from its bed, and not to transitory ischemia. This transient hypertension resulting from nephrectomy must be taken into account in order to avoid erroneous deductions.

The Relation of Renal Artery Ligation to Renal Hypertension and Renal Excretory Insufficiency

The evidence available to date may be briefly summarized as follows:

1. Unilateral nephrectomy does not produce chronic hypertension or gross renal excretory insufficiency (although there is a fleeting hypertension).

2. Unilateral renal artery clamping, when the other kidney is normal, usually produces hypertension of varying duration, but does not produce gross renal excretory insufficiency.

3. Unilateral renal artery clamping followed by removal of the normal kidney usually produces either hypertension, or excretory insufficiency, or both.^{5, 10, 14}

4. Removal of an ischemic kidney, the remaining kidney being normal, results in disappearance of the hypertension and no demonstrable gross impairment of excretory function.^{5, 10, etc.}

5. Bilateral renal artery clamping usually results in hypertension with or without renal excretory insufficiency.²

6. Complete ligation of both renal arteries causes hypertension and renal excretory insufficiency; in the terminal stages the hypertension may disappear.^{27, 5}

7. Bilateral nephrectomy causes only renal excretory insufficiency (excepting for a fleeting neurogenic hypertension).

8. Complete occlusion of both the renal artery and vein causes *only* renal excretory insufficiency.^{5, 10}

9. Ligation of the renal vein causes renal insufficiency and may produce hypertension.²⁸

10. Ureteral obstruction causes renal excretory insufficiency with or without hypertension.^{10, 26}

11. Charcoal injected into the renal arteries produces multiple emboli, resulting in renal excretory insufficiency without hypertension.²⁹

12. Trypsin injected into the renal arteries produces focal necrosis, resulting in chronic renal insufficiency with a transitory hypertension only during the acute inflammatory stage.³⁰

13. Removal of almost all the kidney substance or partial occlusion of the arterial supply to both kidneys results in excretory insufficiency with or without hypertension.²⁵

These experimental facts can be readily accounted for on the following assumptions:

1. The origin of the fleeting hypertension caused by nephrectomy is different from that of the other forms of renal hypertension as outlined above.

2. Renal hypertension is produced whenever the ratio of ischemic kidney substance to normally functioning kidney substance exceeds a certain value. This critical ratio can be produced when ischemic kidney tissue is present (a) by removing normal kidney substance, as by nephrectomy, destruction by emboli, or trypsin necrosis, etc., as well as by (b) increasing the amount of ischemic kidney substance. The greater ease of producing hypertension when the kidney's excretory ability or reserve is hampered is thus accounted for. It would appear that there is an optimum degree of ischemia favorable to the production of hypertension, and that this is not dependent on the interference with excretory ability is shown by the results obtained following unilateral clamping. The primary mechanism of renal hypertension thus appears to be the presence of a critical amount of ischemic renal substance, the quantity being secondarily determined by the number of normally functioning excretory units. We feel that the ratio

$$\frac{\text{quantity of ischemic renal tissue}}{\text{quantity of normal renal tissue}}$$

can be less than 1 and still produce hypertension, since persistent hypertension can occur after unilateral renal clamping with the other kidney normal.⁵

3. Renal excretory insufficiency is unrelated to hypertension, and occurs whenever the total number of excretory units is reduced below a critical level (about $\frac{1}{3}$ of the normal total number of excretory units has been found to be the limit below which gross excretory insufficiency appears^{31, 32}). Chronic renal excretory insufficiency without chronic hypertension has been produced.^{29, 30, 5, 25}

These three working hypotheses are in accord with the work reported to date. Studies in this field should logically be directed to determine (1) the details of the mechanisms whereby renal ischemia leads to hypertension, (2) the ways in which ischemia of the kidneys is produced clinically, and (3) what can be done to counteract or remove the influence of the ischemic kidney.

SUMMARY

1. The genesis of the hypertension following renal ischemia (Goldblatt method) was reinvestigated in an attempt to demonstrate a humoral mediator in hypertensive animals.

2. The average femoral arterial blood pressure of 127 normal trained dogs, determined by the Hamilton technique, was 155/80 mm. Hg. The average brachial arterial blood pressure of 16 normal trained dogs, determined indirectly, was 130/85 mm. Hg.

3. The hypertension which developed in unilaterally nephrectomized animals was more severe and of longer duration than in those animals having a second normal kidney; 50 per cent of these animals died in uremia.

4. Bilateral partial renal arterial occlusion was performed in 24 dogs, of which 85 per cent developed hypertension. This was more severe and longer in duration than when partial occlusion of only one renal artery was produced. The nonprotein nitrogen of the blood usually became elevated following clamping, and 7 dogs died in uremia.

5. The severity and persistence of the effects of renal ischemia depend on the presence of a normal kidney. This indicates that hypertension depends on the ratio of ischemic to normal renal tissue.

6. Distemper was found to cause an alleviation or disappearance of renal hypertension; the hypertension recurred when the distemper was cured.

7. Partial thyroparathyroidectomy did not affect the blood pressure in renal hypertension.

8. Histologic examination of ischemic kidneys in which ischemia had been present as long as 6 months failed to reveal any definite abnormalities.

9. Cross-transfusion of several liters of whole blood for 18 or more hours between trained unanesthetized dogs with persistent renal hypertension and trained unanesthetized bilaterally nephrectomized non-hypertensive dogs failed to reveal any pressor response in the non-hypertensive dog.

10. Perfusion of large quantities of heparinized blood over several hours from an anesthetized dog with persistent renal hypertension into the isolated denervated hind-limb preparation failed to reveal any vasopressor action.

11. A temporary hypertension lasting several hours was found to follow uni- or bilateral nephrectomy. This did not occur in control, mock operations. It is suggested that the transient hypertension following nephrectomy is neurogenic in origin.

We are indebted to the various members of the department who have assisted, especially with the perfusion and cross-transfusion experiments.

REFERENCES

1. Cash, J. R.: A Preliminary Study of the Blood Pressure Following Reduction of Renal Substance, With a Note on Simultaneous Changes in Blood Chemistry and Blood Volume, *Bull. Johns Hopkins Hosp.* 35: 168, 1924.
2. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension. I. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, *J. Exper. Med.* 59: 347, 1934.
3. Goldblatt, H., Gross, J., and Hanzal, R. F.: Splanchnic Section in Experimental Hypertension, *Am. J. Path.* 12: 760, 1936.
4. Goldblatt, H.: Studies on Experimental Hypertension. III. The Production of Persistent Hypertension in Monkeys (Macaque) by Renal Ischemia, *J. Exper. Med.* 65: 671, 1937.
5. Goldblatt, H.: Studies on Experimental Hypertension. V. The Pathogenesis of Experimental Hypertension Due to Renal Ischemia, *Ann. Int. Med.* 11: 69, 1937.
6. Goldblatt, H., and Wartman, W. B.: Studies on Experimental Hypertension. VI. The Effect of Section of Anterior Spinal Nerve Roots on Experimental Hypertension Due to Renal Ischemia, *J. Exper. Med.* 66: 527, 1937.
7. Collins, D. A.: Hypertension From Constriction of the Arteries of Denervated Kidneys, *Am. J. Physiol.* 116: 616, 1936.
8. Page, I. H.: Relationship of Extrinsic Renal Nerves to Origin of Experimental Hypertension, *Am. J. Physiol.* 112: 166, 1935.
9. Freeman, N. E., and Page, I. H.: Hypertension Produced by Constriction of the Renal Artery in Sympathectomized Dogs, *AM. HEART J.* 14: 405, 1937.
10. Block, A., and Levy, S. E.: Studies on the Etiology of Renal Hypertension, *Ann. Surg.* 106: 826, 1937.
11. Houssay, B. A., and Fasciolo, J. C.: Demonstracion del Mecanismo Humoral de la Hypertension Nefrogena, *Boletin de la Academia Nacional de Medicina*, p. 342, Sept. 24, 1937.
12. Ferris, H. W., and Hynes, J. F.: Indirect Blood Pressure Readings in Dogs: Description of Method and Report of Results, *J. Lab. & Clin. Med.* 16: 597, 1930-31.
13. Hamilton, W. F., Brewer, G., and Brotman, I.: Pressure Pulse Contours in the Intact Animal, *Am. J. Physiol.* 107: 427, 1934.
14. Katz, L. N., Mendlowitz, M., and Friedman, M.: A Study of the Factors Concerned in Renal Hypertension, *Proc. Soc. Exper. Biol. & Med.* 37: 722, 1938.
15. Goldblatt, H.: Studies on Experimental Hypertension. VII. The Production of the Malignant Phase of Hypertension, *J. Exper. Med.* 67: 809, 1938.
16. Page, I. H., and Sweet, J. E.: Extirpation of Pituitary Gland on Arterial Blood Pressure of Dogs With Experimental Hypertension, *Proc. Soc. Exper. Biol. & Med.* 34: 260, 1936.
17. Glenn, F., and Lasher, E. P.: Effect of Total Thyroidectomy Upon Production and Maintenance of Experimental Hypertension, *Proc. Soc. Exper. Biol. & Med.* 38: 158, 1938.
18. Child, C. G.: Observations on the Pathologic Changes Following Experimental Hypertension Produced by Constriction of the Renal Artery, *J. Exper. Med.* 67: 521, 1938.
19. Elaut, L.: Observations Concernant l'Hypertension Chronique Expérimentale du Chien par Constriction de l'Artère Rénale, *Compt. rend. Soc. de biol.* 123: 1244, 1936.
20. Prinzmetal, M., Friedman, B., and Rosenthal, N.: Nature of Peripheral Resistance in Arterial Hypertension, *Proc. Soc. Exper. Biol. & Med.* 34: 545, 1936.

21. Page, I. H.: Vasopressor Action of Extracts of Plasma of Normal Dogs and Dogs With Experimentally Produced Hypertension, *Proc. Soc. Exper. Biol. & Med.* 35: 112, 1936.
22. Collins, D. A., and Hoffbauer, F. W.: Effect of Transfusion of Blood From Dogs With Experimental Renal Hypertension Into Normal Dogs, *Proc. Soc. Exper. Biol. & Med.* 35: 539, 1937.
23. Pickering, G. W.: The Effect of Introducing Blood From Patients With Essential Hypertension Into Other Human Subjects, *Clin. Sc.* 2: 185, 1936.
24. Scott, D. A., and Charles, A. F.: Studies on Heparin. III. The Purification of Heparin, *J. Biol. Chem.* 102: 437, 1933.
25. Wood, J. E., Jr., and Cash, J. R.: Experimental Hypertension—Observations on Sustained Elevation of Systolic and Diastolic Blood Pressure in Dogs, *J. Clin. Investigation* 15: 543, 1936.
26. Harrison, T. R., Mason, M. F., Resnik, H., and Rainey, J.: Changes in Blood Pressure in Relation to Experimental Renal Insufficiency, *Tr. A. Am. Physicians* 51: 280, 1936.
27. Cash, J. R.: Further Studies on Arterial Hypertension, *Proc. Soc. Exper. Biol. & Med.* 23: 609, 1926.
28. Bell, E. T., and Pedersen, A. H.: The Causes of Hypertension, *Ann. Int. Med.* 4: 227, 1930.
29. Jensen, C. R., and Apfelbach, C. W.: Experimental Infarction of the Glomeruli in Dogs. II. Blood Pressure in Chronic Renal Insufficiency, *Arch. Path.* 13: 255, 1932.
30. Friedman, M., and Katz, L. N.: Renal Insufficiency Following Trypsin Injection Into the Renal Arteries, *J. Exper. Med.* 68: 485, 1938.
31. Bradford, J. R.: The Results Following Partial Nephrectomy and the Influence of the Kidney on Metabolism, *J. Physiol.* 23: 415, 1898-99.
32. Pearce, R. M.: The Influence of the Reduction of Kidney Substance Upon Nitrogenous Metabolism, *J. Exper. Med.* 10: 632, 1908.

THE SUPERNORMAL PHASE OF RECOVERY IN MAN*

D. SCHERF, M.D., NEW YORK, N. Y., AND A. SCHOTT, M.D.,
LONDON, ENGLAND

THE two cases described in this report seem to demonstrate the presence of a "supernormal phase" of recovery in the human heart. According to Adrian and Keith Lucas,¹ the supernormal phase is a temporary overswing of the recovery curve of excitable tissue after the transmission of an impulse; during this phase, stimuli of an intensity which at any other time would be subliminal become effective.

Since very few cases illustrating the characteristics of supernormal phase in man have been published, and since this interpretation has been contested by competent authorities in some of them, the report of two additional cases seems warranted.

CASE 1 (Fig. 1) is one of partial heart block with dropped beats; right axis deviation is present. The tracings were sent to us for examination some time ago and, unfortunately, the clinical data are not available.

In this and subsequent tracings the P-P, R-R, P-R and R-P (or P-Q and Q-P) intervals were measured, and expressed in hundredths of a second. The P-waves are numbered consecutively. The mechanism of the underlying rhythm is illustrated by means of accompanying keys. Since the P-waves were not infrequently fused with preceding T-waves, accurate measurements could not be made in some cycles. However, on no occasion does the error exceed 0.03 second. This does not invalidate either the interpretation or the conclusions drawn relative to the underlying mechanism.

Fig. 1A (Lead I) shows that the sinoauricular rate varies very little (P-P = 0.50-0.56 second; rate = 107-120 beats per minute). The tracing comprises thirteen ventricular complexes with sixteen P-waves, three of which (the fifth, tenth, and fourteenth) are blocked. Whereas in the usual case of dropped beats a gradual lengthening of the P-R interval leads up to the dropped beat, the increase of the second over the first P-R interval being greater than the increase of the third P-R interval over the second, conditions in this case are different. There is no gradual lengthening of the P-R interval. At the beginning of the tracing (Fig. 1A), P-1 is fused with the T of the preceding ventricular complex and conducted with a P-R interval of 0.34 second. The next P, P-2, occurs much earlier in diastole, i.e., only 0.10 second after the beginning of the preceding initial ventricular complex and hence definitely before the beginning of T. Accordingly, one should expect that P-2 would be conducted more slowly than P-1, but actually its conduction time is shorter

*From the New York Medical College and Flower Hospital, and Guy's Hospital, London.

Received for publication Aug. 15, 1938.

Fig. 1B obviously illustrates the same situation as Fig. 1A. In Fig. 1C the P-waves are not quite so distinct, but their position can be determined with a degree of accuracy sufficient to show that the same conditions prevail. The sixth P-wave is blocked; P-7 comes after a P-P interval of 0.56 second and follows the preceding Q-wave after 0.80 second; on the other hand, P-2 follows Q-2 after the lapse of only 0.14 second, but is conducted with a P-Q interval of only 0.30 second. The three auricular impulses having the shortest conduction times (P-2, P-5, and P-10, 0.30, 0.28, and 0.29 second, respectively) are precisely the impulses which follow the preceding QRS-complexes after the shortest intervals (0.12-0.14 second). Here again, as far as the position of the P-waves can be ascertained, it seems that the earlier the P-wave occurs in diastole the shorter its A-V conduction time. The only blocked P-wave in Fig. 1C (P-6) occurs late in diastole (Q-P interval approximately 0.25 second).

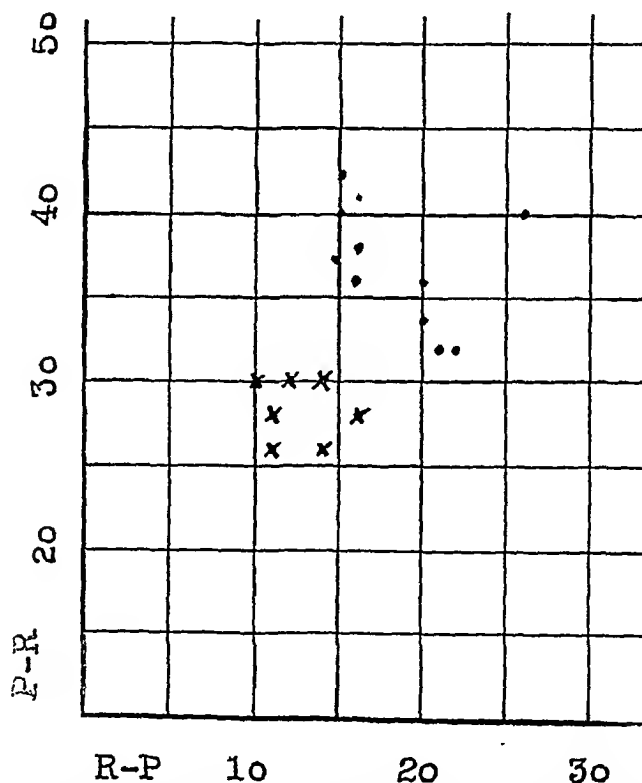


Fig. 2.—P-waves occurring earlier in diastole (shorter R-P distance) are followed by a shorter conduction time to the ventricle (shorter P-R); short R-P intervals and short P-R intervals (x); long R-P intervals and longer P-R intervals (.).

In Fig. 2 the relations between the R-P and the following P-R intervals are shown diagrammatically by plotting the R-P intervals as abscissas against the P-R intervals as ordinates. The only figures employed were those obtained when accurate measurements could be secured. It will be noted that *short* R-P intervals, i.e., of less than 0.15 second, are para-

doxically followed by short P-R intervals, up to 0.30 second (\times), whereas after long R-P intervals (0.15-0.26 second) the P-R intervals range from 0.32 to 0.41 second (.).

Accordingly, all three records show that auricular impulses occurring early in diastole are frequently conducted in a shorter time than those occurring late in diastole. Therefore, the length of the preceding recovery period cannot be the sole factor determining the length of the following P-R interval. Moreover, contrary to usual experience, those auricular impulses which are blocked are usually not those which occur earliest in diastole, but latest. The fact that the auricular impulses which occur after equal R-P intervals are sometimes blocked and sometimes conducted is easily understood, since variations in the tone of the extra-cardiac nerves and in the excitability of the muscle³ are known to produce this in the various ordinary types of partial auriculoventricular block.

Accordingly, the principal features of this case can be summarized as follows: In a case of sinoauricular rhythm with partial heart block and dropped beats, eight auricular impulses occurring 0.15 to 0.26 second after the preceding ventricular beat are blocked, whereas forty-two sinoauricular beats occurring 0.10 to 0.26 second after the preceding ventricular beat are conducted. Those beats which show an unexpected decrease in the conduction time occur earliest in diastole (Q-P or R-P intervals, 0.10 to 0.14 second). These facts seem to warrant the conclusion that in this case there was a supernormal phase of recovery for P-waves occurring 0.10 to 0.14 second from the beginning of the preceding QRS-complex.

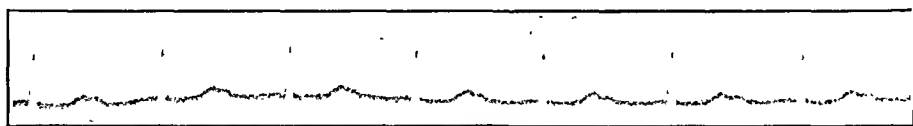


Fig. 3.—Case 2. Prolonged P-R interval.

CASE 2 (Figs. 3 and 4).—The tracings were secured from an eighteen-year-old man suffering from myocarditis following tonsillitis. Several electrocardiograms showed merely sinus rhythm with lengthened auriculoventricular conduction time (P-R interval = 0.31 second, Fig. 3). Upon one occasion only were conditions found similar to those evident in Case 1 (Fig. 4).

This is also a case of partial heart block with dropped beats. The P-P intervals can be accurately measured at various places and the sinoauricular rhythm is found to vary but little (P-P = 0.55-0.64 second; rate = 93-109 beats per minute). By measuring this distance backward and forward from distinct P-waves, the position of those P-waves which

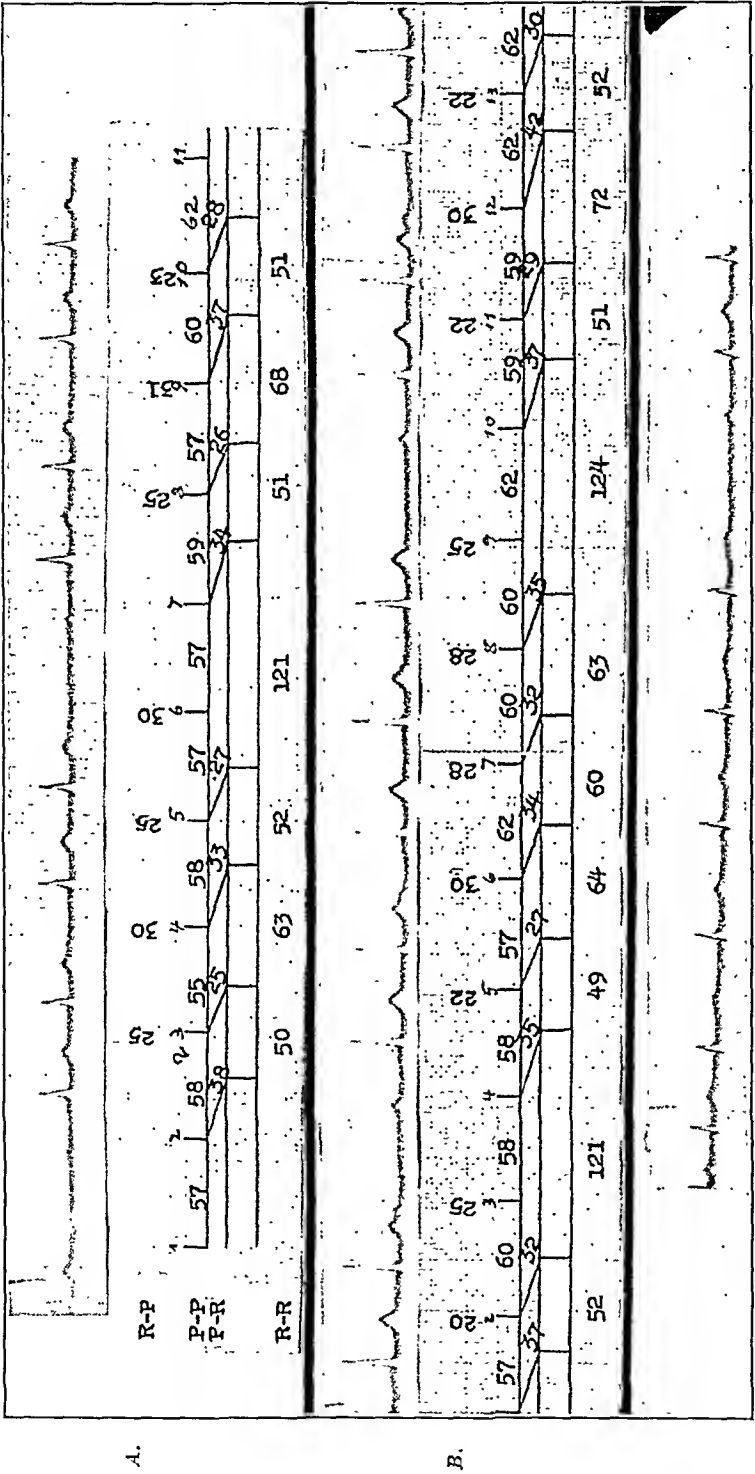


Fig. 4.—Case 2. Dropped beats (Wenckebach's periods). Some P-waves coming early in diastole are followed by abnormally short A-V conduction time.

are fused with T-waves can be interpolated in this manner with a fair degree of accuracy.

The sixth P-wave (P-6), following 0.30 second after the preceding ventricular complex, is blocked; P-7, coming 0.57 second after P-6 and 0.87 second after the preceding ventricular complex, is conducted with the long P-R interval of 0.34 second; however, the next sinoauricular impulse (P-8) occurs about 0.25 second after the preceding QRS and is conducted much faster (P-R = 0.26 second). Here again, the earlier in diastole a conducted sinoauricular impulse occurs, the faster it seems to be conducted. For example, P-3, coming after an R-P interval of 0.25 second, is conducted in 0.25 second, whereas P-4, which occurs 0.30 second after the preceding ventricular complex, shows a P-R interval of 0.33 second.

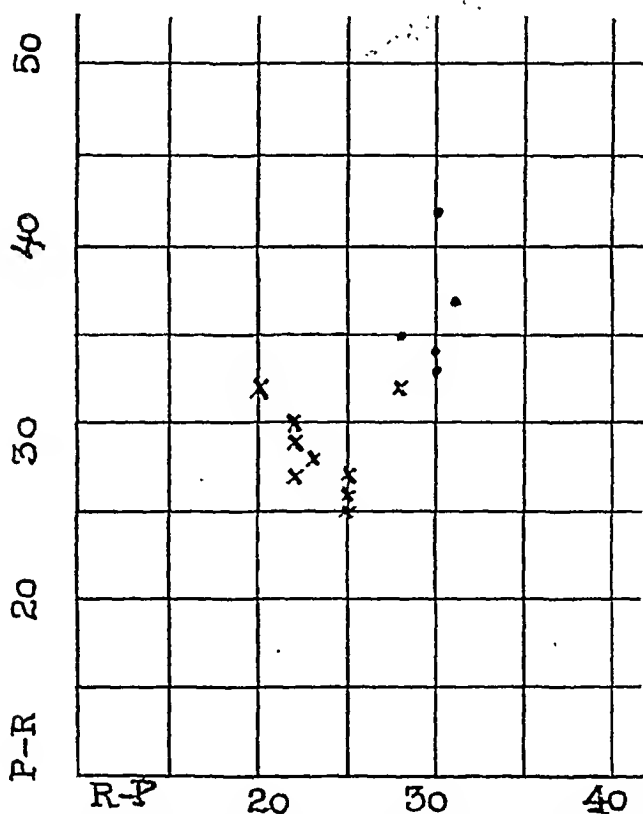


Fig. 5.—P-waves appearing earlier in diastole are paradoxically followed by shorter auriculoventricular conduction time. See Fig. 2 for symbols.

Lead II (Fig. 4B) shows the same situation very clearly. The third P-wave (P-3) is blocked; therefore, P-4 occurs after a long period of recovery but is conducted with the long P-R interval of 0.35 second. The next sinoauricular impulse (P-5), occurring after the short R-P interval of 0.22 second, is conducted with a P-R interval of only 0.27 second; but the next P-wave (P-6), coming later in diastole (R-P = 0.30 second), is conducted much more slowly (P-R = 0.34 second). The last six beats exhibit even greater variations in the same sense. The ninth P-wave

(P-9) is blocked; P-10, coming after a long period of recovery, is conducted slowly ($P-R = 0.37$ second). The subsequent P-waves reveal the following time relationships: P-11 ($R-P = 0.22$ second; $P-R = 0.29$ second), P-12 ($R-P = 0.30$ second; $P-R = 0.42$ second), P-13 ($R-P = 0.22$ second; $P-R = 0.30$ second).

Since many of the P-waves are fused with T-waves, too much importance cannot be attached to the figures themselves, but the condition of conduction and of the subsequent P-R intervals can be definitely ascertained and is strikingly similar to that in Case 1. The phenomenon must be interpreted in the same way, namely, as indicative of the presence of a supernormal phase of recovery affecting, in this case, impulses occurring from 0.22 to 0.25 second after the beginning of the preceding QRS-complex.

The diagram of Fig. 5 (Case 2) demonstrates clearly that short R-P intervals are followed paradoxically by short P-R intervals (x), whereas the auriculoventricular conduction time after a longer diastole is usually much longer (.).

DISCUSSION

The two cases described are both examples of partial heart block with dropped beats showing certain peculiarities not commonly observed in such cases. In a great majority of instances of dropped beats, the omitted beat is preceded by a series of contractions exhibiting gradually increasing P-R intervals; the first beat conducted after the dropped beat exhibits the shortest P-R interval.² Moreover, with rare exceptions,^{4, 5} the increase of the second P-R interval over the first is considerably greater than the third over the second. The explanation of this peculiar manner of increase of P-R intervals in the usual case of dropped beats lies in the fact that the refractory period of the first beat after the pause, which is stronger than the others owing to the longer period of recovery, is longer than that of succeeding weaker ones, so that the second impulse meets tissues of considerably reduced responsiveness. This explanation is based upon experimental observations regarding the relation between the length of the refractory period and the length of the preceding rest period;^{6, 7} it is supported by the clinical observation that in some cases of partial heart block with gradually lengthening P-R intervals and dropped beats the second ventricular complex, and this one alone, may exhibit an abnormal shape owing to aberrant intraventricular conduction.⁸

A comparison between the two cases under discussion and the usual variety of partial heart block with dropped beats reveals a fundamental difference, namely, that in the two cases not only was the dropped beat never foreshadowed by gradually lengthening P-R intervals, but the first conducted impulse after the dropped beat was transmitted with a longer

P-R interval than some of the succeeding ones; impulses falling early in diastole were conducted while those which were blocked occurred much later in diastole. Moreover, the earlier in diastole a sinoauricular impulse occurred, the shorter its conduction time usually was. This peculiar condition seems to us to be susceptible of explanation only by assuming that in these two cases a supernormal phase of recovery was present in early diastole during which an impulse yielded a response; impulses falling later in diastole, and therefore after the supernormal phase, were below threshold and failed to elicit a response. Only after a long recovery period, created by the dropped beat, could the next impulse be transmitted to the ventricles; but the lengthened P-R intervals of those beats are indicative of the extent to which the responsiveness of the tissues was impaired.

A linear relationship between the R-P and the P-R intervals could not be traced in every instance. However, reference was made earlier to the fact that variations in the tone of the extracardiac nerves and in the excitability of the muscle are responsible for this alteration.

A supernormal phase in the recovery curve was first described by Adrian and Keith Lucas¹ with regard to nerve fibers, and later by Adrian⁹ in the case of cardiac muscle under definite experimental conditions (perfusion with a relatively acid fluid); this was confirmed by Wastl¹⁰ and later by Gayda.¹¹ The absolute refractory period after the transmission of an impulse is followed by a relative refractory period during which the tissues, at first, respond only to strong stimuli and subsequently, gradually, to weaker ones; but under certain conditions this recovery curve shows a temporary overswing. During this phase the tissues will respond to stimuli which would be subliminal at any other time. Consequently this phase was called the "supernormal phase." Ashman¹² demonstrated the presence of a supernormal phase of recovery in the compressed turtle heart, and Isayama¹³ reported it in the recovery of the swallowing center. Junkmann⁷ found that the supernormal phase in the frog heart is followed by a subnormal phase and that recovery of conductivity shows similar oscillations, although the peak of the "supernormal phase" is always below the normal resting level. Lewis and Master,¹⁴ however, failed to find a supernormal phase in the dog's heart, and Schellong⁶ pointed out that the decrease of excitability and conductivity of the heart after a longer standstill and their gradual increase during the next few beats must be distinguished from a true supernormal phase.

The number of observations indicating the presence of a supernormal phase in man is very small. Lewis and Master¹⁵ and Ashman and Herrmann¹⁶ have published electrocardiograms showing conducted sinoauricular beats during one part of early diastole only, which they interpreted as indicating the presence of a supernormal phase. However, Wenneke-

bach and Winterberg⁵ showed that the cases of Lewis and Master and Case 1 of Ashman and Herrmann could be interpreted as instances of dissociation with interference between a faster atrioventricular rhythm and a partially blocked sinoauricular rhythm, the effective rate of the latter being slower than the atrioventricular rate, owing to the partial block, and that it was unnecessary to assume a supernormal phase in these cases.

Luten and Pope¹⁷ published a case of 3:1 block in which sinoauricular impulses were conducted when they occurred in a "critical zone." They explain this phenomenon by assuming a temporary increase of excitability of the ventricles, the cause of which remains obscure. In Wolferth's case¹⁸ of varying degree of heart block only those P-waves which occurred 0.45-0.70 second after the beginning of the preceding QRS were followed by QRS-complexes. While rejecting the assumption of a supernormal phase of recovery, this author explains this phenomenon by postulating (1) a prolongation of the rest period in the block area prior to transmission produced by the meeting of an idioventricular impulse and an auricular one, and (2) a transient improvement of the nutrition of the area of block as the result of ventricular systole and increased blood flow. The latter would be analogous to the shortening of those interauricular intervals in cases of complete heart block during which an idioventricular beat occurs. Jervell's patient¹⁹ showed, at times, partial heart block and, at other times, complete heart block with occasionally conducted sinoauricular beats; only those P-waves which followed 0.50-0.55 second after the beginning of the preceding ventricular complex were conducted.

Jervell points out that in his case a supernormal phase is much more probable than dissociation with interference between an atrioventricular and a partially blocked sinoauricular rhythm (5:1 block in his Fig. 2, irregular block in his Fig. 1), although the latter interpretation cannot be absolutely dismissed.

In the two cases under discussion, the assumption of a supernormal phase seems to us the sole satisfactory explanation. Obviously, these cannot be cases of dissociation with interference, for this would not explain the fact that P-waves occurring early in diastole are conducted, whereas those coming later may be blocked; moreover, it would not account for the longer interventricular intervals seen in Case 1 (those intervals are almost three times as long as the preceding P-R intervals). Nor can the explanation advanced by Wolferth for his case be applied since there is no complete block in our cases. Our interpretation of these cases as examples of the presence of a supernormal phase is based upon the following points:

1. Only those P-waves which occurred over a limited period of early diastole were followed by a ventricular response, whereas sinoauricular impulses occurring later in diastole were sometimes blocked.

2. When the P-waves were sufficiently distinct to allow accurate measurements to be made it was found that, within certain limits, the earlier in diastole the sinoauricular impulses occurred, the shorter the P-R intervals with which they were conducted. The P-R intervals of beats occurring very early in diastole were considerably shorter than the P-R intervals of the beats which occurred after a dropped beat. The same relationship also seemed to exist when accurate measurements were impossible owing to fusion of the P-waves with the preceding T-waves, but when the position of the P-waves could be ascertained with a fair degree of accuracy because of the constant auricular rate.

3. The usual lengthening of the P-R intervals leading up to a dropped beat was never observed in our cases.

4. Alternative explanations, advanced in the literature for similar though not identical cases, were shown to be inapplicable to the two cases under discussion since the cases reported by others might be interpreted as examples of dissociation with interference in the presence of partial block.

5. In experimental studies the supernormal phase was noted when the tissues were surrounded by a relatively acid fluid; on the other hand, it has been shown that the rate of propagation of the excitatory process in perfused hearts of terrapins and dogs²⁰ and in the mammalian auricle²¹ is decreased by relatively acid perfusates. In both of our cases the A-V conduction was greatly depressed, as shown by the considerable lengthening of the P-R intervals of the beats following a dropped beat. Although the assumption of an increased acidity of tissue fluids must remain hypothetical, it would be one factor which might account for the presence of a supernormal phase as well as for the lengthening of the P-R intervals of beats occurring after a long period of recovery.

A discussion of the question of which property of the heart shows the supernormal phase, i.e., whether it is the excitability of the muscle or a special quality, "conductivity," is not contemplated. Following Lewis,²² the writers prefer for the present to sum up those properties in the general term, tissue responsiveness.

SUMMARY

Two cases of partial heart block with dropped beats are described. They present the unusual feature that auricular impulses occurring at a certain early phase of diastole were conducted faster than those which occurred later in diastole. Those auricular impulses which were blocked occurred late in diastole and, within certain explicable limits, later than the conducted impulses. This phenomenon is explained by assuming a supernormal phase of recovery.

REFERENCES

1. Adrian, E. D., and Keith Lucas: On the Summation of Propagated Disturbances in the Nerve and Muscle, *J. Physiol.* 44: 68, 1912.
2. Wenckebach, K. F.: Zur Analyse des unregelmässigen Pulses, *Ztschr. f. klin. Med.* 37: 475, 1899.
3. Trendelenburg, W.: Untersuchungen über das Verhalten des Herzmuskels bei rhythmischer elektrischer Reizung, *Arch. f. Physiol.* 271, 1903.
4. Rothberger, C. J.: Normale und pathologische Physiologie der Rhythmik und Koordination des Herzens, *Ergebn. d. Physiol.* 32: 472, 1931.
5. Wenckebach, K. F., and Winterberg: Die unregelmässige Herztätigkeit, pp. 310 and 336, Leipzig, 1927, Wilhelm Engelmann.
6. Schellong, F.: Die Refraktärphase der Erregungsfortpflanzung im normalen und digitalvergifteten Herzmuskel; Untersuchungen über die Grundeigenschaften des Herzmuskels, *Ztschr. f. d. ges. exper. Med.* 78: 1, 1931.
7. Junkmann, K.: Beiträge zur Physiologie und Pharmakologie der Erregbarkeit des Froschherzens, *Arch. f. exper. Pharmakologie Pathologie und Pharmakologie* 108: 149, 313, 1925.
8. Scherf, D.: Über intraventrikuläre Störungen der Erregungsausbreitung bei den Wenckebachschen Perioden, *Wien. Arch. f. inn. Med.* 18: 403, 1929.
9. Adrian, E. D.: The Recovery Process of Excitable Tissues, *J. Physiol.* 54: 1, 1920.
10. Wastl, H.: Die übernormale Phase der Erholung des Herzmuskels nach einer Systole, *Ztschr. f. Biol.* 75: 289, 1922.
11. Gayda, T.: Sulla fase supernormale del istabilimento del cuore dopo la sistole, *Arch. di sc. biol.* 9: 1, 1926. (Quoted from *Kongresszentralblatt f. d. ges. inn. Med.* 45: 886, 1927.)
12. Ashman, R.: Conductivity in Compressed Cardiac Muscle; Supernormal Phase in Conductivity in Compressed Auricular Muscle of Turtle Heart, *Am. J. Physiol.* 74: 140, 1925.
13. Isayama, S.: Nachweis einer übernormalen Phase des Schluckzentrums nach dem Schluckakt, *Ztschr. f. Biol.* 82: 339, 1924-25.
14. Lewis, T., and Master, A. M.: Conduction in Mammalian Heart; A-V Conduction, *Heart* 12: 209, 1925.
15. Lewis, T., and Master, A. M.: Supernormal Recovery Phase, Illustrated by Two Clinical Cases of Heart-Block, *Heart* 11: 371, 1924.
16. Ashman, R., and Herrmann, G. R.: Supernormal Phase in Conduction and Recovery Curve for Human Junctional Tissues, *AM. HEART J.* 1: 594, 1926.
17. Luten, D., and Pope, S., Jr.: Variations in Heart Block Sometimes Attributed to Supernormal Recovery Phase, *AM. HEART J.* 5: 570, 1930.
18. Wolferth, C. C.: So-Called Supernormal Recovery Phase of Conduction in Heart Muscle, *AM. HEART J.* 3: 706, 1928.
19. Jervell, A.: Nachweis einer "supernormalen Reizbarkeitsphase" in einem Falle von partiellem Block, *Acta med. Scandinav. Supp.* 59: 626, 1934.
20. Andrus, E. C., and Carter, E. P.: The Development and Propagation of the Excitatory Process in the Perfused Heart, *Heart* 11: 97, 1923.
21. Drury, A. N., and Andrus, E. C.: Influence of Hydrogen-Ion Concentration Upon Conduction in Auricle of Perfused Mammalian Heart, *Heart* 11: 389, 1924.
22. Lewis, T.: The Mechanism and Graphic Registrations of the Heart Beat, p. 381, London, 1925, Shaw & Sons, Ltd.

Department of Clinical Reports

MYXEDEMA WITH MULTIPLE SEROUS EFFUSIONS AND CARDIAC INVOLVEMENT (MYXEDEMA HEART)

CASE REPORT*

EUGENE R. MARZULLO, M.D., AND SAVERIO FRANCO, M.D.
BROOKLYN, N. Y.

THE following case of myxedema is being reported because the patient had pericardial and pleural effusion and ascites with cardiac involvement (myxedema heart) and was successfully followed over a period of ten years.

L. M. M., a white woman, 48 years old, was first admitted to the Long Island College Hospital Feb. 11, 1927, and thereafter was readmitted on six other occasions. On the first admission she complained of cough, shortness of breath, and early fatigue. She had been incapacitated for four months. As an adult, she was well until 1922. At this time she was in Scotland and there she sought medical aid because of weakness, shortness of breath, and swelling of the abdomen. Five abdominal paracenteses were done in a period of one year and each time about sixteen pints of fluid were removed. She improved, and on being discharged was told that she had "liver trouble." Her family history was irrelevant. She was married at the age of 24 years and had three normal pregnancies and one spontaneous miscarriage. No history of venereal infection. Her menopause occurred at the age of 47 years without unusual symptoms.

Physical Examination on the first admission to the Long Island College Hospital revealed a moderately well-nourished woman 48 years of age. Her temperature was 98° F., her pulse rate 76, her respiratory rate 20, and her blood pressure 165/110. The left border of cardiac dullness was in the midaxillary line and the right border of dullness 5 cm. from the midline in the fourth right intercostal space. On the left side of the lower thorax there was dullness with tubular breathing. The edge of the liver was 9 cm. below the costal margin. The abdomen was full. Dullness was present in both flanks and a fluid wave was elicited. There was no edema of the extremities.

The erythrocyte count was 4,600,000, the hemoglobin 80 per cent, and the total and differential leucocyte counts normal. The blood Wassermann reaction was negative. Examination of the urine and chemical examination of the blood showed nothing abnormal. The total serum protein was 6.40%, the serum albumin 3.79%, and the serum globulin 2.61%. A roentgenogram of the thorax suggested the presence of pericardial effusion. Pericardial paracentesis was done and 240 c.c. of a straw-colored fluid were removed. The specific gravity was 1.018; there were 400 cells per c.mm., 99 per cent of which were lymphocytes. This fluid was sterile and guinea pig inoculation revealed no tubercle bacilli. The patient improved and left the hospital March 6, 1927.

*From the department of Medicine of Long Island College Hospital.
Received for publication Aug. 13, 1938.



Fig. 1.—Patient L. M. on June 11, 1932.

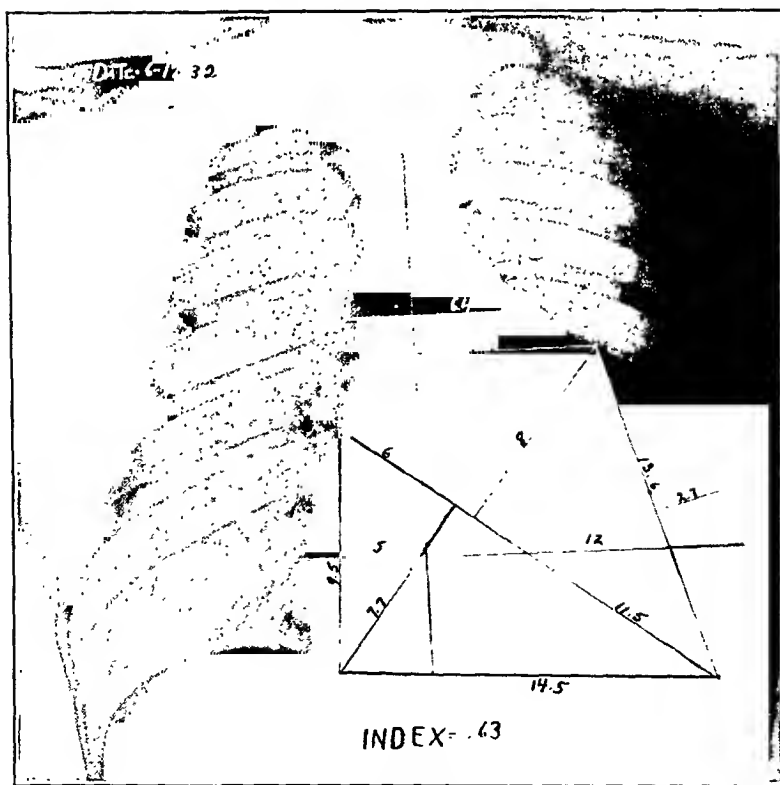


Fig. 2.—Teleoroentgenogram taken June 17, 1932.

Three weeks later she was readmitted because of a recurrence of her complaints and, in addition, swelling of the abdomen. Signs of pericardial effusion were again present. The liver extended 6 cm. below the costal margin and again an abdominal fluid wave was obtained. There was no edema of the legs. The hemoglobin was 58% and the erythrocyte count 2,500,000. The urine contained a trace of albumin but no sugar; its specific gravity was 1.022; the microscopic examination was negative. A roentgenogram of the thorax again confirmed the presence of pericardial effusion; 1200 c.c. were removed, and the fluid was found to have a specific gravity of 1.022 and an albumin content of 50 grams per liter. Culture of this fluid revealed no growth, and a guinea pig inoculation was negative. The abdominal fluid disappeared with salyrgan therapy. The patient was discharged improved.

On June 5, 1927, she was readmitted because of recurrence of swelling of the abdomen, shortness of breath, swelling of the thighs, and weakness. Moderate edema of the face was present. Evidence of pericardial effusion and ascites was again present, and a pericardial paracentesis yielded 1200 c.c. of a straw-colored fluid which was sterile on culture and negative on guinea pig inoculation. Salyrgan was administered for the ascites. The patient improved and was discharged on June 18.



Fig. 3.—Patient L. M. on Oct. 5, 1934.

The fourth admission took place on Aug. 8, 1927. Symptoms and signs similar to those on previous admissions were present. This time a pericardial tap yielded 1600 c.c. of a straw-colored fluid; the specific gravity was 1.020, and it contained 2600 cells per cubic millimeter, 96 per cent of which were lymphocytes. This fluid contained 32 gm. of albumin per liter; it was sterile on culture, and a guinea pig injected with it remained well. The patient was discharged in a few days but was readmitted Oct. 4, 1927, at which time 2300 c.c. of fluid were removed from the right pleural cavity. Salyrgan was administered for the ascites.

In June, 1932, she was readmitted to the hospital. At this time she showed impaired hearing, a mild degree of alopecia, and a dry, thin, wrinkled, aged-looking skin. The transverse diameter of the heart was found to measure 10 cm. in the fifth intercostal space. The heart sounds were faint and short. There was no evidence of pericardial fluid. The liver was palpable 3 cm. below the costal border. A telorocentgenogram at this time showed the heart to be moderately enlarged; this enlargement was left-sided, involving the left ventricle and left auricle. The hemo-

globin was 65 per cent, and the blood cholesterol 357 mg. per 100 c.c. The basal metabolic rate was minus 50 per cent. At this time it was recognized that the patient was suffering from hypothyroidism, and it was conceived that all of her past symptoms and signs might have been manifestations of myxedema. The experimental work of Tatum,¹ and of Goldberg,² gave support to this idea, and the patient was placed on thyroid therapy. On June 25, 1932, thyroid gland, in doses of 1 grain

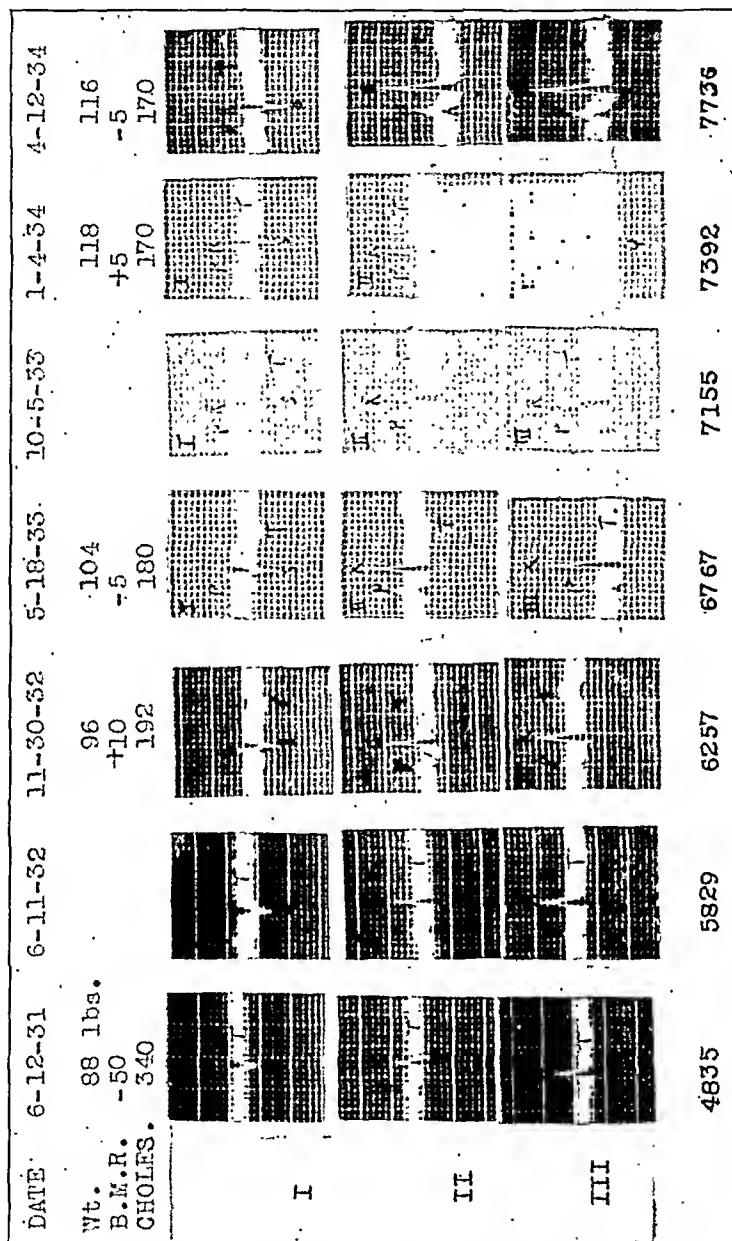


Fig. 4.

three times per day, was given. Later the dose was increased to $1\frac{1}{2}$ grains three times per day, and 2 grains three times per day and on July 20 it was increased to 3 grains three times per day. In thirty days the patient stated that she felt better than she had in years. By July 2 the pulse rate had increased to 120 and the patient complained of headache and epigastric distress. The dose of thyroid substance was reduced for two days and on July 4 it was discontinued until July 13.

The basal metabolic rate on July 6 was minus 5 per cent. An electrocardiogram showed but little improvement. On July 11 the blood cholesterol was 170 mg. per cent. On July 13 thyroid therapy was resumed in doses of 1 grain, three times per day. The basal metabolic rate on this day was minus 16.9 per cent, and on August 6 it was minus 2.6 per cent. When the patient was discharged she was given thyroid gland in doses of $\frac{1}{2}$ grain three times per day, and 30 grains of ferrie and ammonium citrates, three times per day. She continued to take $\frac{1}{2}$ grain of thyroid gland three times per day by mouth, and entered the hospital Nov. 30, 1932, for a comparative study. At this time it was noted that she was greatly improved, her color was better, her hemoglobin was 72 per cent and her hair had

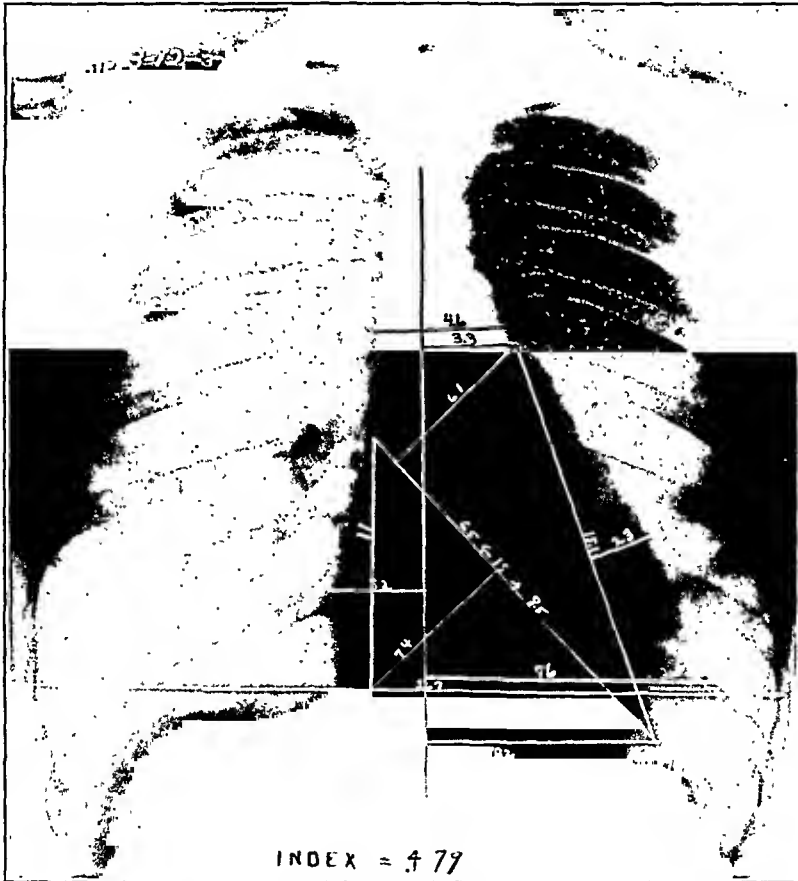


Fig. 5.—Teleoroentgenogram taken March 12, 1937.

grown in and was thick. The skin had lost its thinness and was no longer dry. The edge of the liver could not be felt. A teleoroentgenogram showed no improvement. The electrocardiogram, however, showed improvement, especially in Leads II and III, in which the P- and T-waves were now evident. The basal metabolic rate was plus 10 per cent. The patient was discharged in one day and advised to take $\frac{1}{2}$ grain of thyroid gland, three times per day. She returned in February, 1933, for follow-up study. A teleoroentgenogram showed improvement. The basal metabolic rate on February 25, however, was minus 20 per cent. The dose of thyroid gland was increased to $1\frac{1}{2}$ grains three times per day, and on March 10 the basal metabolic rate was minus 2 per cent. At this time the patient had no complaints, and for the first time in seven years she was able to work and become self supporting. She has maintained this state of health on $\frac{1}{2}$ grain of thyroid extract three times per day, with occasional periods of one to two weeks without any medication.

Experimentally, it has been known for a long time that collections of fluid in serous cavities may occur in thyroidectomized animals.

In 1913, Tatum¹ encountered effusion in the pericardium and peritoneum of thyroidectomized rabbits and, in 1927, Goldberg² reported collections of fluid in serous cavities in thyroidectomized sheep.

The pathology of myxedema heart is not too well defined. We have seen a patient with myxedema die quite suddenly, and post-mortem examination of the heart grossly and microscopically showed a normal myocardium.

Lerman, Clark and Means³ (1933) state that there have been five autopsies on "myxedema heart" patients at the Massachusetts General Hospital. Three died from complicating infections, one died of unknown cause, and one died of arteriosclerotic heart disease. Four showed interstitial edema with more or less fibrosis of the heart muscle, and the fifth showed fibrosis only. Two of their autopsied patients who did not receive thyroid before death had fluid in the pericardial sac. One patient had 150 c.c. and the other had over one liter. They refer to the report of the Clinical Society of London, published in 1888, in which pathologic findings in twenty cases were reviewed. One-third had left ventricular hypertrophy, one-half had arteriosclerosis. In nine cases a microscopic examination was done, and in three of these there was interstitial myocarditis. Goldberg² (1927) reported on seventeen animals thyroidectomized at birth and autopsied after one to two years. He found ascites, anasarca, hydrothorax, hydropericardium, passive congestion of lungs and liver, and arteriosclerosis. The hearts were dilated, pale, and flabby. There was disintegration of the heart muscle fibers. From these findings the factors present in myxedema heart can be the following: (1) interstitial edema, (2) fibrosis, (3) pericardial effusions.

It should be noted that not every patient with myxedema develops myxedema heart. Fahr⁴ (1932) states that out of seventeen cases of severe and moderately severe myxedema, only thirteen (75 per cent) showed symptoms and signs of heart involvement.

COMMENT

It is interesting to note that this patient, when first seen, was considered to have Piek's disease. Tuberculosis of serous membranes was considered and disproved by the fluid examinations, the negative results of guinea pig inoculations, and the clinical course. Cirrhosis of the liver was considered but could not be substantiated. There can be little doubt that this case was one of severe myxedema. Whether the effusions found in such cases are the direct result of congestive heart failure or are an exudative accumulation from myxedema per se has been questioned. In this case congestive heart failure did not exist and it could not therefore play a significant part in the production of the serous effusions. The

serum proteins were normal. The fact that the effusions recurred until adequate thyroid therapy was established suggests that myxedema alone was the principal factor in this case.

The development of ascites in early life, at the age of 32 years, with subsequent effusion in the pericardium and pleura, and the successful ten year follow-up study are important, and allow a clearer understanding of the clinical course of myxedema. The importance of hypothyroidism as a possible etiological factor in the differential diagnosis in such cases is emphasized.

In this case the high blood cholesterol (340 mg. per 100 c.e.) became normal (180 mg.) after approximately one and a half years of thyroid therapy. The electrocardiogram became normal after almost three years of treatment and the heart size did not become normal until six years of treatment had elapsed.

CONCLUSION

A case of severe myxedema is presented in which there were the usual signs of myxedema heart and polyserous effusions. The patient has been under treatment for ten years and continues to be well. The effusions occurred in the absence of significant congestive heart failure and it is suggested that myxedema per se was the cause of the effusions.

The authors express grateful thanks to Dr. Alexis Mays of Brooklyn for his cooperation in the interpretation of the electrocardiograms, and to Dr. A. L. L. Bell of Brooklyn for his kind help in the study of the teleoroentgenograms.

REFERENCES

1. Tatum, A. L.: Studies in Experimental Cretinism, With Suggestions as to a Biological Test for Thyroid Secretion, *Proc. Am. Physiol. Soc.*, Boston, p. 23, 1912-13.
2. Goldberg, S. A.: Changes in Organs of Thyroidectomized Sheep and Goats, *Quart. J. Exper. Physiol.* 17: 15, 1927.
3. Lerman, J., Clark, R. J., and Means, J. H.: The Heart in Myxedema, Electrocardiogram and Roentgen-Ray Measurements Before and After Therapy, *Ann. Int. Med.* 6: 1251, 1933.
4. Fahr, George: Myxedema Heart. A Report Based Upon a Study of 17 Cases of Myxedema, *AM. HEART J.* 8: 91, 1932.

MYOCARDIAL INFARCTION WITH RUPTURE OF THE SEPTUM

REPORT OF A CASE*

ROY W. SCOTT, M.D., AND CURTIS F. GARVIN, M.D.

CLEVELAND, OHIO

LATHAM,¹ in 1845, was the first to describe rupture of the infarcted septum of the heart. From time to time others have described the clinical and pathologic features of this condition so that Sayer,² in 1934, was able to collect seventeen cases, to which he added one more. Since then Kepler, Berkman and Barnes,³ Master and Jaffe,⁴ Nadler,⁵ Mahrburg,⁶ Biekel and Mozer,⁷ Huber,⁸ Gross and Schwartz,⁹ Stern,¹⁰ and Stanley¹¹ have reported additional cases.

In only three cases of rupture of the infarcted septum has the correct diagnosis been made during life.¹¹ Most of the errors have probably been due to lack of familiarity with the condition. Briefly, the symptoms and signs are those of myocardial infarction plus the distinguishing findings of an interventricular septal defect. The picture of myocardial infarction is well known and need not be described. Since the intraventricular pressure is higher in the left than in the right ventricle, patency of the septum permits the passage of blood between the two chambers during systole and causes a loud systolic murmur over the whole precordium, often accompanied by a palpable thrill.

CASE REPORT

C. M., a 56-year-old white man, American, entered the Cleveland City Hospital Jan. 17, 1931. He had been in good health until Jan. 3, 1931 (two weeks before admission), when he suddenly became dizzy and fell over unconscious. He remained unconscious for two days. Subsequently he was completely disoriented and had various delusions and hallucinations. He was accordingly admitted to the psychopathic division for observation and treatment.

General physical examination at the time of admission gave essentially negative results except that there was evidence of rather marked arteriosclerosis. The heart was normal. The blood pressure was 135/90.

On neurological examination, the pupils were large and equal but did not react to light or in accommodation, and the consensual reflex was absent. The muscles supplied by the oculomotor nerve were paralyzed on the right and were weak on the left. The tendon reflexes were slightly increased on the left and there was a questionable hyperesthesia of the right side of the face.

The Wassermann reaction on the blood and the spinal fluid was negative.

It was felt that the patient had generalized arteriosclerosis, arteriosclerotic dementia, and vascular thrombosis with encephalomalacia in the midbrain.

*From the Department of Medicine of Cleveland City Hospital and the School of Medicine of Western Reserve University.

Received for publication Aug. 29, 1938.

The hospital course was uneventful until Feb. 21, 1931, when the patient was found to have a temperature of 39° C. and a respiratory rate of 40 per minute. No history could be obtained from the patient. Examination at this time failed to disclose the cause of the fever and increased respiratory rate.

Four days later, February 25, râles were found at the bases of the lungs, and the patient was considered to have bronchopneumonia. The temperature remained at 39° C. and the respiratory rate was 30 per minute.



Fig. 1.—Photograph of left ventricle with arrow indicating the septal defect.

On March 2, over the entire precordium there was heard a loud systolic murmur which was transmitted to the base of the heart and to the left axilla. The murmur lasted throughout systole and was accompanied by a palpable thrill. The thrill was very accessible and the murmur was intense. At this time there were signs of consolidation at the right base. The leucocyte count was 22,400 per cubic millimeter.

The blood pressure was 98/60. The temperature continued to average 39° C. and the respiratory rate varied between 40 and 50 per minute.

It was believed that the patient had bronchopneumonia and, associated with this, bacterial endocarditis of the aortic valve.

Blood cultures were taken but showed no growth. The patient died March 12, 1931, twenty days after the onset of his acute illness.

The final clinical diagnoses were: Generalized arteriosclerosis; arteriosclerotic dementia; vascular thrombosis with encephalomalacia in the midbrain; bronchopneumonia, right lower lobe; acute bacterial endocarditis involving the aortic valve.

A post-mortem examination was performed the day following death. The heart weighed 550 gm. The right auricle showed many marantic thrombi. There was an irregular funnel-shaped hole in the anterior portion of the interventricular septum approximately midway between the apex and the base (6 cm. from the apex). This fistula between the ventricles measured 1.1 cm. in its anteroposterior dimension and 1.8 cm. in its vertical dimension on the left ventricular side (Fig. 1). The opening on the right ventricular side was roughly circular and measured 1 cm. in diameter (Fig. 2). The edges of the lesion consisted of necrotic muscle tissue. The entire area of necrosis was roughly circular and measured 3 cm. in diameter. Anteriorly, the area extended through to the epicardial surface over the interventricular septum.



Fig. 2.—Photograph of right ventricle with arrow indicating the septal defect.

The coronary arteries all showed marked arteriosclerosis, which was so severe as to cause occlusion of the right posterior descending ramus, but no thrombus was present.

The brain showed three areas of encephalomalacia, none of which exceeded 1 cm. in any dimension. They were located in the anterior portion of the thalamus, in the posterior pole of the corpus striatum, and in the pons. The cerebral arteries were markedly sclerotic. There was an infarct in the lower lobe of the right lung.

Microscopic examination of the interventricular septum revealed large areas in which the muscle fibers had lost their characteristic staining affinities. The nuclei were pale-staining, pyknotic, and in places showed karyorrhexis. There were areas of acute necrosis and of leucocytic infiltration. The cellular infiltrations were like-

wise undergoing necrosis. The vessels in the section showed moderate thickening of the walls, especially of the intima. The lesion was definitely that of acute infarction.

The final pathologic diagnoses were: Generalized arteriosclerosis, moderate; coronary sclerosis, severe, with occlusion of posterior descending ramus; acute myocardial infarction of interventricular septum with fistula formation between right and left ventricles; cerebral arteriosclerosis, severe; multiple areas of encephalomalacia; cardiac hypertrophy and dilatation; pulmonary artery thrombosis; pulmonary infarct, right lower lobe.

COMMENT

This case was very characteristic of rupture of the infarcted interventricular septum. The condition is rare and usually not recognized clinically, but nevertheless is susceptible of diagnosis if it is remembered that the symptoms and signs are those of myocardial infarction plus those of an interventricular defect.

REFERENCES

1. Latham, P. M.: Lectures on Subjects Connected with Clinical Medicine Comprising Diseases of the Heart, vol. 2, p. 168, London, 1845, Longmans, Brown, Green & Longmans.
2. Sayer, R. V.: Perforation of the Infarcted Interventricular Septum, *Arch. Int. Med.* 53: 140, 1934.
3. Kepler, E. J., Berkman, J. M., and Barnes, A. R.: Acute Myocardial Infarction with Rupture of the Septum, *Proc. Staff Meet., Mayo Clinic* 10: 209, 1935.
4. Master, A. M., and Jaffe, H. L.: Acute Coronary Artery Occlusion with Perforation of the Interventricular Septum, *J. Mt. Sinai Hosp.* 2: 182, 1935.
5. Nadler, R.: Perforation of Interventricular Septum, *Ztschr. f. Kreislaufforsch.* 27: 689, 1935.
6. Mahrburg, S.: Perforation of Ventricular Septum—Chronic Course, *Frankfurt. Ztschr. f. Path.* 47: 552, 1935.
7. Biekel, G., and Mozer, J. J.: Perforating Infarction of Interventricular Septum—Two Cases, *Bull. et mém. Soc. méd. d. hôp. de Paris* 51: 1564, 1935.
8. Huber, H.: Acquired Defect of Interventricular Septum, *Ztschr. f. Kreislaufforsch.* 27: 825, 1935.
9. Gross, H., and Schwartz, S. P.: Acquired Interventricular Septal Defect, *AM. HEART J.* 11: 626, 1936.
10. Stern, N. S.: Rupture of Interventricular Septum: Case, *Memphis M. J.* 11: 35, 1936.
11. Stanley, D. F.: Acquired Interventricular Septum Defect, *AM. HEART J.* 14: 240, 1937.

Department of Reviews and Abstracts

Selected Abstracts

Gregg, Donald E., and Dewald, Donald: **The Immediate Effects of the Occlusion of the Coronary Veins on Collateral Blood Flow in the Coronary Arteries.** *Am. J. Physiol.* 124: 435, 1938.

It has been established after acute coronary sinus ligation that:

The peripheral coronary backflow is markedly elevated in the ramus descendens anterior (up to 39 c.c. per min.), but not in the right coronary.

The maximum retrograde flow is reached in from ten to thirty minutes and following sinus release does not immediately return to the control backflow figure (maximum of approximately 1.0 c.c. per minute).

The blood is highly unsaturated, containing only 3 to 4 volumes per cent oxygen.

Such a volume of blood with its low oxygen content is not sufficient to prevent failure of contraction when central occlusion of a coronary ramus is added to sinus ligation and hence is of no material value to the potentially infarcted myocardial area.

AUTHORS.

Hübener, G.: **Intraventricular Conduction Defects.** *Deutsche med. Wchnschr.* 64: 1222, 1938.

This is a report of 66 cases of intraventricular conduction defects. The old terminology is used in classifying the location of the lesion.

	WOMEN	MEN
Right-sided bundle branch block	3	19
Left-sided bundle branch block	0	1
Incomplete double-sided block	1	24
Transition between complete and incomplete block	2	16
	—	—
	6	60

The author fails to understand the difference between sexes.

The age incidence was 45 to 85 years, except one woman who was 35 years old.

CASES		CASES	
No symptoms	7	Blood pressure above 230	4
Dyspnea	5	Blood pressure, 160 to 230	32
Congestive cough	2	Blood pressure, 130 to 159	22
Angina pectoris	28	Blood pressure below 130	8

Twenty-four patients showed no changes in x-ray shadow.

The form of the block did not seem to affect mortality. Three cases had been observed forty-five to forty-eight years, twelve cases, thirty-six months.

For therapy, digitalis was used, only reluctantly and in minimum doses. Quinidine was given prophylactically against auricular fibrillation and flutter.

JENSEN.

Enghoff, H., and Liedholm, K.: **Concerning Cheyne-Stokes Breathing.** Upsala läkaref. förh. 44: 1, 1938.

A historical survey shows that the phenomenon has especially been studied by Traube and by Filehne. The literature on the symptomatology is fully discussed. Cheyne-Stokes breathing occurs in direct injury to the brain, especially the medulla, as a result of breathing air poor in oxygen, in hibernating animals, in children just as they are about to go to sleep, also during sleep at a certain depth, both physiologic and when produced by drugs. It occurs in degenerative heart disease, valvular heart disease, and in many diseases involving the central nervous system, including diabetic and uremic coma. The various attempts at explaining Cheyne-Stokes breathing are discussed; it may be an exaggeration of a normal phenomenon.

Cheyne-Stokes phenomenon involves respiration, circulation, and the central nervous system. Respiratory phases alternate with periods of apnea; the change between the two is gradual, and when respiration is most intense, the expiratory effort is diminished. The onset of the respiratory phase is more abrupt than its cessation. When the respiratory phases are measured with the subsequent periods of apnea the entire period is more constant than when they are measured with the preceding periods. These facts indicate that the period begins with the respiratory phase. There is a definite negative correlation between the respiratory phase and the subsequent interval, but no correlation between the respiratory phase and the preceding interval. This finding is tested statistically. This is contrary to the usual relationship between hyperpnea and apnea, and they can, therefore, not be cause and effect. During the respiratory periods, hyperventilation is produced by increase in the number of respirations, not by increasing the depths of the individual respirations. Blood pressure and electrocardiogram are not affected by Cheyne-Stokes respiration. Carbon-dioxide and oxygen inhalations and metaphyllin will sometimes relieve the symptom.

The authors conclude that the respiratory change is the primary factor and that the cause is in the respiratory center. Perhaps there is an inherent rhythm of the center, normally under control of higher centers, but occasionally dissociated therefrom.

JENSEN.

Robb, Jane Sands, and Robb, Robert C.: **Localization of Cardiac Infarcts in Man.** Am. J. M. Sc. 197: 7, 1939.

This review of the published cases of various authors illustrates the essential agreement between the topographic (anterior and posterior) and the specific (muscle bundle) methods of localization. Among the cases surveyed, there are no glaring discrepancies, i.e., no anterior or posterior localization which could not equally well be explained by muscle bundle localization. On the other hand, instances are quoted where the muscle bundle localization would reconcile published discrepancies, e.g., right or left, and the "confusing cases" discussed by various authors. The muscle bundle method offers four specific types of electrocardiograms and a basis for analysis of combined lesions, whereas the T_1 , T_2 method of classification is shown not to include all the commonly found combinations and moreover, T_1 , T_2 classifications are not necessarily mutually exclusive.

AUTHORS.

Robb, Jane Sands, and Robb, Robert C.: **Localization of Cardiac Infarcts in Man.** Am. J. M. Sc. 197: 17, 1939.

The T_1 , T_2 method of localization is valuable where infarcts occur in the more common localities, and under these conditions there is close agreement with the muscle bundle method.

Numerous authors report difficulty in localization when the infarcts involve an unusual site. When a reciprocal relation of T_1 to T_2 is lacking, application of this principle becomes difficult. It is shown that this reciprocal relation often is lacking.

The muscle bundle method of localization, supported by experimental work, has been applied to the analysis of seventy-seven cases, forty-eight with adequate autopsy reports from literature and twenty-nine new reports. When one of the four characteristic electrocardiograms appears there is no doubt as to the muscle involved, but to specify which portion, or the extent of the lesion, or the cause of the disturbance in conduction within the one muscle bundle is not possible.

A short review of the superficial and deep bulbo- and sinospiral muscles together with their function and blood supply is offered.

As a "thumbnail" diagnostic method one may ignore Lead II and note that $R-T_1$ depression indicates involvement of the superficial bulbospiral muscle; if $R-T_2$ is depressed the deep sinospiral must be implicated; and superficial sinospiral lesion raises both $R-T_1$ and $R-T_2$ above the iso-electric level. $R-T$ takeoff from the peak of R (or near the peak) in all leads, especially in the presence of low voltage, indicates a deep bulbospiral lesion. Inequality of the R bases is to be sought and its presence is more instructive than its amplitude.

Clinical findings may fortify the experimental conclusions and the electrocardiographic interpretation in the following respects: Severe pain is often present when the superficial muscles are involved, and if the lesion is anterior a friction rub may be heard. Deep muscle injuries precipitate large and abrupt falls of blood pressure associated with variegated and atypical pain sensations generally accentuated by effort.

Inference as to etiology from the electrocardiogram alone is not justified, since many different pathologic changes may result in a similar effect on conduction.

Displacements of $R-T$ do not disappear as rapidly clinically as when infarction is experimentally produced by ligating a vessel in an otherwise normal heart, for seldom does one find in man occlusion of one vessel without disturbance of the collateral circulation (Gross and Calef).

We confirm the findings of Harris and Hussey and of Gross and Calef, modifying the conclusion of the latter to read "occlusion of the left anterior descending coronary artery *proximal to the branch to the deep sinospiral and distal to the origin of the circumflex branch* results in $R-T_1$ elevation and $R-T_2$ depression." It is shown that this type of record can be obtained from right and from posterior lesions as well.

The superficial muscles may be infarcted repeatedly and death may ensue when a deep muscle is eventually involved, or from some noncardiac cause.

The prognosis for deep sinospiral lesions is graver and treatment of an attack should be more rigid and much more prolonged.

Infarcts of the deep bulbospiral are even more serious and often result in sudden death.

AUTHORS.

Hedley, O. F.: Incidence of Rheumatic Heart Disease Among College Students in the United States. Public Health Reports 53: 1635, 1938.

Among 104,163 student health examinations in eighty-six colleges and universities in the United States, 1,207 cases of rheumatic heart disease, a rate of 11.6

per 1,000, were reported. Among 63,828 men students, 607 cases, or 9.5 per 1,000, were reported, while among 40,335 women students, 600 cases, or 14.9 per 1,000, were indicated.

The reported incidence of rheumatic heart disease showed an inverse relationship to the size of the college or university and the number of student health examinations reported.

In fourteen large universities with affiliated medical schools reporting at least 1,500 student health examinations, and where student health services are affiliated with the American Student Health Association, among 46,098 student health examinations 296 cases were reported—an incidence of 6.4 per 1,000.

It is doubtful whether sex is an important factor in the incidence of this disease among college students.

In contradistinction to adult type pulmonary tuberculosis, the reported incidence of rheumatic heart disease is lower in institutions with well-organized health services. The problem in rheumatic heart disease is not primarily case-finding but the detection and interpretation of physical signs.

While it is suggested that persons with physical signs suggesting heart disease or having past histories of rheumatic infection be subjected to complete cardiovascular surveys, there is no objective method for the mass diagnosis of rheumatic heart disease comparable to tuberculin testing and x-raying the chest for the detection of adult type pulmonary tuberculosis. The diagnosis of rheumatic heart disease is dependent in a large measure on the interest, skill, and experience of the individual examining physician. For this reason, the services of well-qualified consultants should be obtained wherever feasible to pass upon doubtful cases and to evaluate the functional status of known cases.

To a certain extent it is almost inevitable that more diagnoses of heart disease are made in smaller institutions. Even under the most favorable circumstances it is difficult to evaluate certain physical signs suggesting heart disease.

An unwarranted diagnosis of heart disease may seriously affect a student's career, both in college and in later years. Painstaking examinations and kindly reassurance are necessary to dispel cardiac neuroses.

In the diagnosis of rheumatic heart disease it should be borne in mind that it is an acquired condition due to an infection. In most cases where a significant history and physical signs are indicative of this disease, the examination should be interpreted in the light of the past and present history of rheumatic infection, together with its influence upon functional capacity.

AUTHOR.

Baker, Thomas W., and Willius, Fredrick A.: Coronary Thrombosis Among Women. *Am. J. M. Sc.* 196: 815, 1938.

Only two striking differences were noted in coronary thrombosis among women, as compared with men. The first is its relative infrequency among women; the ratio of men to women approximates 7 to 1. The second striking difference is the tendency for the disease to occur later in life among women; the average age of women was 6 years greater than the average age of men. The relatively late appearance in life is presented more vividly if one recalls the fact that, in this series of cases, coronary thrombosis was recorded in 89 per cent of the cases in which women were between the ages of 50 and 80 years and in 79 per cent of cases in which men were of the same age. It appears justifiable, therefore, to assume that women are less susceptible to the development of coronary thrombosis than are men, and that when it occurs among women, it tends to occur later in life.

The association of hypertension, diabetes mellitus, and other conditions appears only to bear a relationship compatible with the predominant age periods represented by the group of patients included in this study.

AUTHORS.

de Boer, S.: *Researches on the Electrocardiogram*. *Cardiologia* 2: 292, 1938.

Lewis' theory of limited potential differences was criticized by experiments.

By experiments it was demonstrated that it is impossible to determine the direction of the contraction wave through the heart by Lewis' method.

According to Craib a monophasic curve can be produced only (1) if the heart is suspended in the air, (2) if the excitation wave passes under one electrode, (3) if the impulse dies out at a region exhibiting conspicuous injury current. This theory is not right, in all three respects. De Boer obtained monophasic curves during the small alternating systoles (therefore without injury current) with indirect lead (the excitation wave, therefore, does not pass under one electrode). The hearts were left in situ (therefore, not suspended in the air).

The ventricular electrogram of extrasystoles and the after-retardation of the excitation wave are rendered intelligible in the light of the interference theory.

The author demonstrated that it is only possible to explain all the known facts if one accepts the interference theory.

AUTHOR.

Grossman, Edward B., and Williams, John R., Jr.: *Relation of Age to Renal Pressor Substance*. *Arch. Int. Med.* 62: 799, 1938.

Extracts containing renal pressor substance (renin) were administered to rats of various ages in doses proportional to the body surface. The youngest rats (6 to 10 weeks old) showed the least rise in blood pressure; the oldest (2½ years) displayed the greatest pressor effect, and intermediate responses were displayed by rats of intermediate age (6 months to 2 years). On the other hand, the youngest rats had the most pressor substance in their own kidneys, and the oldest rats had the least.

The greater sensitivity of the oldest animals to renal pressor substance did not appear to be dependent on a general increase in reactivity to all pressor agents, for the administration of epinephrine produced as great a rise in blood pressure in the young as it did in the older animals.

The experiments suggest a possible relation between the increased sensitivity of senile rats to renal pressor substance and the tendency of elderly persons to show hypertension. However, it is concluded that no convincing evidence of such a relation exists at present.

AUTHORS.

Massie, Edward, Ethridge, Clayton B., and O'Hare, James P.: *Thiocyanate Therapy in Vascular Hypertension*. *New England J. Med.* 219: 736, 1938.

Sodium thiocyanate was administered according to the method of Barker under carefully controlled conditions to fourteen patients suffering from uncomplicated vascular hypertension.

Prior to the administration of sodium thiocyanate all direct therapy was discontinued and control observations were made for three months. There followed a test period of like duration during which a 5 per cent solution of sodium thiocyanate in syrup of wild cherry was given orally. This interval was followed by another control period of three months during which the syrup alone was administered in comparable dosage.

The dosage was controlled by the blood cyanate concentration, the optimum level of which was found to range between 5 and 7 mg. per cent. The daily amount of sodium thiocyanate which produced and maintained this level varied for different patients.

A lowering blood pressure was obtained in every case. The average fall ranged from 66 to 21 mm. systolic and 33 to 8 mm. diastolic.

Marked symptomatic relief, especially of headache, nervousness, and vertigo, was obtained in twelve of the patients.

Toxic symptoms observed were occasional episodes of transient weakness and infrequent attacks of mild epigastric distress. In addition, nausea, vomiting, and marked weakness occurred in one patient and three attacks of angina pectoris in another.

The authors conclude that thiocyanate therapy constitutes a useful remedy for the treatment of uncomplicated vascular hypertension, provided dosage can be properly controlled by means of blood-cyanate determinations.

This method necessitates careful selection, observation, and regulation of the patient. The extent of its clinical application to the treatment of vascular hypertension is somewhat limited by these requirements.

NAIDE.

East, Terence, and Barnard, W. G.: Pulmonary Atresia and Hypertrophy of the Bronchial Arteries. *Lancet* 2: 834, 1938.

Two cases of complete pulmonary atresia in patients reaching adult life are described. In these patients the bronchial arteries were the only channel for the blood to the lungs, for the ductus arteriosus was closed.

Two other published cases are quoted for comparison. The possibility of the diagnosis of pulmonary atresia according to the physical signs is suggested.

AUTHORS.

Suzman, M. M., Freed, C. C., and Prag, J. J.: Studies on Experimental Peripheral Vascular Disease, With Special Reference to Thromboangiitis Obliterans. *South African J. M. Sc.* 3: 29, 1938.

The etiology of thromboangiitis obliterans with special reference to the role of vasospasm in the genesis of the disease is considered and the similarity of the lesions of Buerger's disease to the trophic changes produced by ergotamine tartrate is pointed out.

Neither a single small (1,000 I. U.) nor a single large dose (100,000 I. U.) of ovarian follicular hormone afforded complete protection against the trophic changes produced by ergotamine tartrate in both male and female rats.

The administration of repeated small doses (500 I. U.) of ovarian follicular hormone completely protected female rats from the trophic changes produced by ergotamine tartrate, whereas in the males only a very slight degree of protection was afforded.

Preliminary castration of male rats did not affect the extent of trophic changes produced by ergotamine tartrate.

The administration of ovarian follicular hormone to castrated male rats afforded complete protection against the trophic changes produced by ergotamine tartrate.

The possibility of hormonal influence in the etiology of thromboangiitis obliterans is discussed, consideration being given to the rarity of the disease in female subjects and to the relationship of the ovaries and of ovarian follicular hormone to the blood volume and blood viscosity in human subjects and experimental animals.

Possible reasons are given for the protection afforded to male rats by the combined effect of castration and ovarian follicular hormone.

AUTHORS.

Bazett, H. C.: *The Effect of Heat on the Blood Volume and Circulation.* J. A. M. A. 111: 1841, 1938.

The effects on the blood volume and circulation of high temperatures applied in acute experiments or treatments of short duration are contrasted with those of milder temperatures continued chronically for days. In an analysis of the effects of heat it is necessary to distinguish the parts played by (a) local dilatation in the cutaneous vessels with its accompanying local increases in the rate of flow, capillary pressure, and fluid transudation; (b) compensatory reduction of the vascular bed in areas other than the skin, which allows dilatation in the cutaneous vessels even when the blood volume is unchanged or reduced; (c) increases in blood volume on exposure to heat which form an alternative method of compensation in lieu of vasoconstriction; and (d) alterations in cardiac output.

The part played by each of the factors is discussed in detail. Experiments with steady, moderate, but maintained rise in environmental temperature, similar to that present during the summer, reveal a significant increase in blood volume which apparently is an adaptation to the prolonged peripheral vasodilatation produced by exposure to moderate heat over a period of days.

The importance of these studies is discussed in relation to their application in the use of heat as a form of therapy.

NAIDE.

Roth, Grace M., Williams, Marvin M. D., and Sheard, Charles: *Changes in the Skin Temperatures of the Extremities Produced by Changes in Posture.* Am. J. Physiol. 124: 161, 1938.

Observations of the effects of posture on the skin temperatures of the toes and fingers were made under environmental conditions which did not produce either great vasoconstriction or great vasodilatation of the extremities but which permitted the fingers and toes to act as the fine adjustors in the control of the dissipation of heat from the body. Under environmental temperatures ranging from 23 to 30° C. (73.4 to 86° F.) with the subjects in the basal metabolic state and free from sweating of the extremities, the skin temperatures of the toes and fingers decreased when the extremities were elevated and increased when the extremities were pendent. When the posture of the body was changed from the horizontal, either voluntarily or when placed in an angular position by means of a tilt-table, the skin temperatures of the toes increased, when the body was tilted with the feet downward and vice versa. These results probably are due to changes in the peripheral circulation as a result of changes in hydrostatic pressure.

HINES.

Heim de Balsac, R.: *The Right Auricle.* Fortschr. a. d. Geb. d. Röntgenstrahlen. 57: 73, 1938.

The author presents evidence that the right border of the heart is made up exclusively by the right auricle and the superior and inferior vena cava. A pathologic aorta may encroach upon this border as well as an enlarged left auricle which appears at first at the upper part of the right auricular border, gradually extending downwards as the left auricle increases in size. It seems that the author does not think that it produces any change of the left contour. He explains the pulsations of the kymogram of the lower part of the right border usually ascribed to the right ventricle to an indirect effect. In this area, the right ventricle completely overpowers the auricle, moving that portion of the heart as a whole, completely obliterating the individual right auricular pulsations.

JENSEN.

American Heart Association, Inc.

RADIO CITY

50 WEST 50TH STREET, NEW YORK, N. Y.

DR. WILLIAM J. KERR

President

DR. WILLIAM D. STROUD
Vice-President

DR. HOWARD B. SPRAGUE

Secretary

DR. WALTER W. HAMBURGER
Treasurer

BOARD OF DIRECTORS

DR. T. HOMER COFFEN Portland, Ore.

DR. CLARENCE DE LA CHAPELLE New York City

DR. WALTER W. HAMBURGER Chicago

DR. GEORGE R. HERRMANN Galveston

DR. EMMET F. HORINE Louisville

*DR. WILLIAM J. KERR San Francisco

*DR. EMANUEL LIBMAN New York City

DR. HUGH McCULLOCH St. Louis

*DR. GILBERT MARQUARDT Chicago

*DR. H. M. MARVIN New Haven

*DR. EDWIN P. MAYNARD, JR. Brooklyn

DR. JONATHAN MEAKINS Montreal

*DR. FRANKLIN NUZUM Santa Barbara

DR. STEWART R. ROBERTS Atlanta

DR. WILLIAM H. ROBEY Boston

DR. ROY W. SCOTT Cleveland

*DR. HOWARD B. SPRAGUE Boston

*DR. WILLIAM D. STROUD Philadelphia

DR. LOUIS VIKO Salt Lake City

DR. HOWARD F. WEST Los Angeles

DR. PAUL D. WHITE Boston

DR. FRANK N. WILSON Ann Arbor

DR. CHARLES C. WOLFERTH Philadelphia

*DR. IRVING S. WRIGHT New York City

*DR. WALLACE M. YATER Washington, D. C.

DR. H. M. MARVIN, *Acting Executive Secretary*

GERTRUDE P. WOOD, *Office Secretary*

TELEPHONE CIRCLE 5-8000

THE American Heart Association, sponsor of the first International Health Broadcast, stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is \$5.00 a year and journal membership at \$10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

**Executive Committee.*

The American Heart Journal

VOL. 17

APRIL, 1939

No. 4

Original Communications

CORONARY SCLEROSIS

AN ANALYSIS OF NINE HUNDRED TWENTY-EIGHT CASES

B. J. CLAWSON, M.D.*
MINNEAPOLIS, MINN.

THERE are three conditions frequently associated with angina and sudden death which have to be considered in a study of deaths due to coronary insufficiency. These are aortic stenosis, syphilitic aortitis, and atherosclerosis of the coronary arteries (coronary sclerosis).

About 15 per cent of individuals with aortic stenosis severe enough to cause death die suddenly, and angina is common. The cause of the angina and sudden death in these cases is still a debated question. All theories so far offered to explain the cause assume a coronary insufficiency.

More than 20 per cent of patients with syphilitic aortitis die more or less suddenly, and angina and sudden death are also common in this group. The cause of the angina and sudden death is obvious. The orifices of the coronary arteries are narrowed by intimal thickening of the aorta.

The most common cause of angina and cardiac sudden death, however, is coronary sclerosis of atherosclerotic type with or without coronary thrombosis and infarction. It is with a study of this group that this paper deals.

No attempt is made to review the literature on coronary disease because this has recently been well done by Levy¹ and his coauthors in "Diseases of the Coronary Arteries and Cardiac Pain."

MATERIAL

The cases studied were all autopsy cases and were described in the records of the department of pathology at the University of Minnesota during the years 1910 to 1936, inclusive. Many of the hearts have been restudied. In others the records had to be relied upon, as the hearts had not been preserved. All histologic ma-

*This study was aided by a grant from the Graduate School of the University of Minnesota.

From the Department of Pathology, University of Minnesota.

Received for publication Sept. 29, 1938.

terial was restudied. There were 928 cases for study, but information on the various conditions analyzed was not always available in all cases; hence some of the tables contain less than the total number.

INCIDENCE

White² has observed that coronary sclerosis as a cause of heart disease varies somewhat in its relative incidence in different parts of the world, largely according to the frequency of such other causes as rheumatic heart disease, hypertension, and syphilitic aortitis. He also emphasized the necessity of stating whether we refer to coronary sclerosis of a degree severe enough to cause death or just to the presence of atherosclerosis in the coronary arteries. The latter condition is present in a high percentage of persons, especially in those 40, or more, years old.

In all of the cases included in this study there was severe involvement of the coronary arteries, and death was considered as being due primarily to coronary disease.

The 928 cases in our series constituted 24 per cent of the 3,872 cases of death from noncongenital cardiac disease that occurred in 23,972 autopsies (4 per cent of all deaths in patients above 6 months of age, and 6 per cent of all deaths of patients 40 years old, and above). Since heart disease is the most common cause of death, the importance of coronary sclerosis becomes evident. Dublin³ believes that the incidence of death from coronary disease is increasing.

CLASSIFICATION

On a clinical basis Levy classified patients with coronary sclerosis into five groups: (1) those with no symptoms and sometimes without signs, the latent group; (2) those with congestive heart failure; (3) those with cardiac pain; (4) those with digestive disturbances; and (5) those with thrombosis.

We placed our autopsied patients in two groups: (1) those with hypertension and (2) those without hypertension. The first corresponded in general to Levy's second group, those with congestive heart failure. These included most of the hospitalized patients. Our second group, or those for the most part without hypertension, corresponded in general with Levy's first group, the latent group, or those with no symptoms or signs. Cases which belong in this second class are more frequently seen by the pathologists than by the internists. This type of sudden cardiac death is commonly seen in a coroner's service. These two groups (those with hypertension and those without hypertension) are further analyzed in respect to etiology, outstanding clinical characteristics, and pathologic findings.

ETIOLOGY

The primary exciting cause of coronary sclerosis cannot be stated until the cause of arteriosclerosis is understood. This is far from being known at the present time.

Age.—Coronary sclerosis may be present at a very early age, even as early as a few weeks, but the degree of sclerosis referred to in this discussion is rarely found under 30 years and most of the patients are much older. Table I gives an analysis of 923 cases in regard to age. The greatest number of patients died in the fifth, sixth, seventh, and eighth decades; only six died in the third decade. The youngest was 22 years old. The ages of those in the nonhypertensive group were scattered over a greater range (fourth to ninth decades). The disease is definitely one of adults.

TABLE I

AGES AND SEX OF PEOPLE DYING WITH CORONARY SCLEROSIS (923 CASES)

DECADES	WITH HYPERTENSION				WITHOUT HYPERTENSION			
	MALES		FEMALES		MALES		FEMALES	
3	1	0.2%	0	0%	5	1%	0	0%
4	7	1.5	1	0.2	33	6.5	1	0.2
5	46	11.0	7	1.5	80	15.5	7	1.5
6	85	20.5	18	4.5	135	26.5	16	3.0
7	111	27.0	39	9.5	116	22.5	24	5.0
8	62	15.0	20	5.0	58	11.0	10	2.0
9	14	3.0	3	1.0	14	3.0	9	1.5
10		0.0		0.0	1	0.2		0.0
	326	78.2	88	21.7	442	86.2	67	13.2

Sex.—Males are regularly regarded as being more commonly afflicted with coronary sclerosis than females. In our series of 923 cases (Table I) there were 768 males and 155 females, a ratio of nearly 4.9 to 1. This, however, is not the ratio in the entire population in Minnesota, for in our material in these decades the ratio of males to females coming to autopsy is 2 to 1. As corrected, our ratio of males to females should be 768 to 310, or about 2.5 to 1. It is evident that death from coronary sclerosis must be expected in females.

Hypertension is the most common suggestive etiologic factor in coronary sclerosis. On the other hand, coronary sclerosis of severe grade is frequently seen without any evidence of hypertension. In our study two criteria were used for determining the existence of hypertension: (1) a history of high blood pressure, and (2) cardiac hypertrophy in the absence of valve defect or any other known cause of hypertrophy. Heart weights of 500 gm., or more, in males and 450 gm., or more, in females were the minimum weights regarded as indicating that hypertension had existed. Hearts with weights slightly below these figures probably were also hypertensive hearts, but were not classed as such in this study.

By using these criteria it was found (Table II) that 418 (45 per cent) of the 928 patients with coronary sclerosis had hypertension; 510 (55 per cent) were placed in the nonhypertensive group. But it is quite evident from the weight of the hearts that many in the latter group also probably had hypertension. In 224 of these 510 the hearts

of the males weighed 400 gm., or more, and of the females 350 gm., or more. Considering these as probable hypertensive cases the number of patients with hypertension is raised to 642, or 69 per cent of the entire group of 928. This incidence of hypertension with coronary sclerosis (69 per cent) is practically the same as was previously estimated from another series by a study of heart weights and the presence of arteriosclerosis in the kidneys.⁴ This high incidence of hypertension with coronary disease appears to be more than a coincidental finding.

TABLE II

FREQUENCY OF HYPERTENSION WITH CORONARY SCLEROSIS (928 CASES)

History, plus, or heart weights 500 gm. or more in males (202) and 450 gm. or more in females (216)	History, minus, or absent with heart weights below 500 gm. in males and 450 gm. in females
418—45 per cent	510—55 per cent
History, plus, or heart weights 400 gm. or more in males and 350 gm. or more in females	History, minus, or absent with heart weights below 400 gm. in males and 350 gm. in females
642—69 per cent	286—31 per cent

CLINICAL CHARACTERISTICS

The clinical considerations noted were duration of symptoms, pain, conditions under which death occurred (effort, rest, etc.) and dyspnea.

Duration.—Adequate histories on duration of symptoms were recorded in 877 of the 928 cases. The duration of symptoms was compared in the hypertensive and nonhypertensive groups. Table III shows the durations as divided into four groups in respect to time: (1) those who died suddenly or who had symptoms lasting but a few minutes; (2) those with symptoms lasting from one hour to one month; (3) those with symptoms lasting from one month to one year; and (4) those who had symptoms lasting from one year to five years, or more.

TABLE III

DURATION OF CLINICAL COURSE IN CORONARY SCLEROSIS (877 CASES)

DURATION	WITH HYPERTENSION		WITHOUT HYPERTENSION		TOTAL	
Sudden to few minutes	52	13.0%	196	41.0%	248	28%
1 hour to 1 month	91	22.5	117	24.5	208	24
1 month to 1 year	108	26.5	73	15.5	181	20.5
1 year to 5 or more years	151	37.5	89	18.5	240	27
	402	99.5	475	99.5	877	99.5

In the first group (those dying suddenly or in a very short time) the manner of death was described by the following terms: "dropped dead," "fell dead," "found dead," and "died in a few minutes." Thirteen per cent of the 402 in the hypertensive group and 41 per cent of the 475 in the group without hypertension were found to have died somewhat suddenly. The frequency of sudden death was considerably greater in

the nonhypertensive group. The number of sudden deaths among those dying in from one hour to one month was about the same in the two groups. As the duration of symptoms increased from one month to one year the percentage ratio of the hypertensive group to the nonhypertensive increased to 26.5 to 15.5. Of those having symptoms from one year to 5 or more years, 37.5 per cent were in the hypertensive group and 18.5 per cent in the nonhypertensive group. It would appear that people dying of coronary sclerosis associated with hypertension tend to have symptoms for a longer time than those without hypertension. In fact, nearly one-half of those without hypertension had no recorded histories.

Pain was the most common symptom recorded. It was localized in different places: heart, chest, precordium, substernal region, epigastrium, abdomen, gallbladder region, retrosternal region, shoulders, gastric area, between the scapulas, back, throat, and posterior part of neck. The pain was described as being referred to shoulders, arms, hands and fingers, hips, legs, elbows, and jaws. It was characterized by the following terms: "cardiac," "tightness in chest," "pressure in chest," "sharp," "cramplike," "viselike," "shooting," "choking," "asthmatic," "constrictive in chest," "numbness," "knifelike," "gastric disturbance," "indigestion," etc.

Pain was recorded as being present in the group with hypertension in 60 per cent of the cases, and absent in 3 per cent (Table IV). No mention of pain was made in 37 per cent. In the group without hypertension, pain was recorded as present in 49 per cent, absent in 1 per cent, and not mentioned in 50 per cent. In the entire number of 928 cases pain was recorded as present in 54 per cent, absent in 2 per cent and not mentioned in 44 per cent. There was a record of pain in more than 50 per cent. It is quite likely that it was present in a larger number, but not recorded. Many of the patients, especially in the nonhypertensive group, died suddenly without any recorded histories.

TABLE IV
FREQUENCY OF PAIN WITH CORONARY SCLEROSIS (928 CASES)

PAIN	WITH HYPERTENSION		WITHOUT HYPERTENSION		TOTAL	
Present	250	60%	251	49%	501	54%
Absent	12	3	6	1	18	2
Not mentioned	156	37	253	50	409	44
Total	418	100	510	100	928	100

Pain was the most constant symptom, but other complaints were of dyspnea and edema, fainting, dizziness, paralysis, gastric distress, symptoms resembling disease of the gallbladder, asthma, rheumatism, etc.

Conditions Under Which Death Occurred.—The way in which death occurred has much importance, especially from a medicolegal point of view. Many terms were used to explain how death occurred in our

cases. The following were some of the most common ones: "fell dead," "dropped dead," "found dead in, going to, or coming from the bathroom," "died suddenly while walking, at work, at home, in hospital, in bed, in automobile, on train, on street, on way to hospital, sitting in a chair, waiting in line for pay check, after putting out washing, putting up stove, following sneezing, on golf course, while digging ditch, in restaurant, running an elevator, after changing an automobile tire, running to catch a streetcar, at a wrestling bout, emptying waste, after struggle, packing for a trip, tripping on rug, picking flowers, in chiropractor's chair, in barber's chair, after eating his wedding dinner, under tree during thunder shower, on way to doctor's office, while delivering a speech, upon receiving a bouquet of flowers from her husband." Many other terms were used, but the foregoing include those relating to effort, rest, emotion, etc.

In analyzing these cases the conditions under which death occurred were placed in the following groups: (1) effort (work, play, other effort); (2) rest (in hospital, at home, in room, in bed, and other rest); and (3) miscellaneous (bathroom, found dead or died suddenly, while eating, with excitement). Eight hundred sixty-seven (867) cases were analyzed (Table V).

TABLE V

CONDITIONS UNDER WHICH DEATH OCCURRED WITH CORONARY SCLEROSIS (867 CASES)

CONDITION	WITH HYPERTENSION			WITHOUT HYPERTENSION			TOTAL	
	21		2.5%	67		7.5%	88	10%
Effort								
work		43%			77.5%			69.5
play		9.5			6.0			7.0
other effort		47.5			16.5			23.5
Rest	328		38%	324		37%	652	75%
hospital		78%			52.5%			65
bed		9			14.0			11.5
room		2			7.0			4.5
home		9			14.0			11.5
other rest		2.5			12.5			7.0
Miscellaneous	34		4%	93		10.5%	127	14.5%
bathroom		20.5%			15%			16.5
found dead								
or sudden		76.5			79.5			78.5
eating		3.0			1.0			1.5
excitement		0			4.5			3.0
Total	383		44.5%	484		55.5%	867	100%
Total noneffort	362		41.5%	417		48%	779	90%

Ten per cent died while engaged in some effort, as work, play, going through a fire test, policeman arresting a man, running up a flight of stairs, changing a tire, running to catch a streetcar, wrestling, packing a suitcase, sneezing, etc. A greater per cent in the nonhypertensive group died while at work, probably because they were able to work. In other forms of effort the greater percentages were in the hypertensive group.

In 75 per cent of the 867 cases analyzed death occurred while the patient was at rest, as in the hospital, in bed, in a room, at home, in a chair, in a sleeping car, in a saloon, in jail, in a doctor's office, picking flowers, in a barber's chair, in an elevator, in a streetcar, in a taxicab, in an automobile, and on a train. The numbers were about equal in the hypertensive and nonhypertensive groups. The greatest number were at rest in the hospital. The final condition which sent the patients to the hospital, except in a very few cases, was not in any way associated with effort. Most of the patients came to the hospital on account of symptoms of congestive heart failure. Some came because of noneardiac conditions, as hypertrophy of the prostate, etc.

Fourteen and one-half per cent of the 867 cases were placed in the miscellaneous group, because the conditions under which these patients died could not be related to effort or rest. There seemed to be a definite relation between going to or coming from the bathroom and coronary attacks. Sixteen and one-half per cent of those in this miscellaneous group died at such a time. Those found dead or those who died suddenly comprised 78.5 per cent of the group. Only a small number died while eating. Excitement seemed to have little to do in precipitating an attack.

It is of interest to note the small number (10 per cent) who died while at work or while engaged in any effort and the larger number (75 per cent) who died while at rest. These facts might have some bearing upon the pathologic physiology concerned in bringing about death in coronary sclerosis. Blood pressure is lower at rest. This might aid in the formation of a thrombus. There appears to be no indication of a tendency for death from coronary occlusion to occur while at work. The contrary is suggested.

The great contrast in the number of those who died while at rest and those who were working (652:88 or 7.4:1) is significant from the standpoint of workmen's compensation. The number dying with effort is probably not more than would be expected under the natural course of events.

PATHOLOGY

The anatomic changes noted in cases of death from coronary disease are for the most part seen best by gross examination, but the minute changes in the vessels and most of the fibrosis of the myocardium require the aid of a microscope. The things observed are atherosclerosis and thrombosis in the vessels, and hypertrophy, fibrosis, infarction, and rupture of the myocardium. Mural thrombosis following infarction is seen on the endocardium. Noninfectious pericardial adhesions, fibrinous and fibrous, are seen over the infarcted areas. There are also the associated pathologic changes, as passive congestion and edema.

Vessels.—The degree of involvement in the left and right coronary arteries is shown in Table VI. The degree of sclerosis is expressed in

grades of + to +++++. Four plus indicates severe thickening and calcification of the coronary arteries, so that the lumens are completely closed as far as can be determined by gross examination. The degree indicated by + is but a slight amount of intimal thickening; ++ and +++ are intermediate stages.

TABLE VI

DEGREE OF SCLEROSIS IN THE CORONARY ARTERIES IN CASES IN WHICH DEATH WAS DUE TO CORONARY SCLEROSIS (900 CASES)

DEGREE OF LEFT AND RIGHT CORONARY SCLEROSIS				WITH HYPERTENSION		WITHOUT HYPERTENSION		TOTAL	
Both	+++	to	++++	244	59.5%	279	57%	523	58%
Left	++++	Right	++	65	15.5	85	17	150	17.5
Left	++++	Right	+	41	10.0	80	16	121	13.0
Left	+++	Right	++	20	5.0	18	3.5	38	4.0
Left	+++	Right	+	17	4.0	15	3.0	32	3.5
Left	++	Right	++	15	3.5	6	1.0	21	2.5
Left	++	Right	+	1	0.2	4	1.0	5	0.5
Right	++++	Left	++	5	1.0	1	0.2	6	0.5
Right	++++	Left	+	2	0.5	2	0.5	4	0.5
Right	+++	Left	++	0	0.0	0	0.0	0	0.0
Right	+++	Left	+	0	0.0	0	0.0	0	0.0
Right	++	Left	+	0	0.0	0	0.0	0	0.0
Total				410	99.2	490	99.2	900	100.0

In 900 cases the description of coronary involvement was complete enough to permit a fairly accurate evaluation of the degree of sclerosis. Fifty-eight per cent showed involvement of +++ to ++++ in both arteries. In 17 per cent there was involvement of +++ in the left coronary and ++ in the right. In 13 per cent it was left ++++ and right +. Involvement of left +++ and right ++ comprised 4 per cent. Left +++ and right + comprised 3.5 per cent. Two and one-half per cent of the patients died with what was estimated as left ++ and right +. Right ++++ and left ++ and right ++++ and left + were small, 0.5 per cent each.

The left coronary artery, generally the anterior descending branch, was the one most severely affected. It was also found that fewer deaths resulted from right arterial involvement than from left, with the same degree of involvement. The percentage of deaths in the hypertensive and nonhypertensive groups with a like amount of arterial change was practically the same.

Thrombosis of one or both coronary arteries is a common complication of coronary sclerosis. Thrombosis of a nonsclerotic vessel is rare. Coronary emboli, except for small emboli in subacute bacterial endocarditis, are also rarely seen. When they do occur there is no relation to coronary sclerosis.

Nine hundred nineteen of our cases were sufficiently well described to determine that coronary thrombosis was present. Thrombosis of one or both coronary arteries was found in 45.5 per cent of the cases (Table VII). It was present in the left artery in 32.5 per cent, in the right in 10 per cent, and in both in 3 per cent of the cases.

TABLE VII

FREQUENCY OF THROMBOSIS WITH CORONARY SCLEROSIS (919 CASES)

ARTERIES	WITH HYPERTENSION (410)		WITHOUT HYPERTENSION (509)		TOTAL	
Left	158	38.5%	143	28%	301	32.5%
Right	48	11.5	43	8.5	91	10
Both	14	3.5	13	2.5	27	3
Total	220	53.5	199	39.0	419	45.5

Thrombosis was more common in the hypertensive group (53.5 per cent) than in the nonhypertensive group (39 per cent). There was gross evidence of thrombosis in less than half of the deaths from coronary disease. Its occurrence was less in the group without hypertension, in which sudden death was more common.

Myocardium.—The pathologic conditions observed in the myocardium were hypertrophy, infarcts, mural thrombi, and areas of fibrosis not due to infarcts. The latter may require microscopic examination for their detection, but gross, irregular areas of fibrosis are not infrequently seen.

Cardiac enlargement was the most common change observed in the myocardium. In speaking of cardiac enlargement it is necessary to know whether enlargement as shown roentgenologically is meant, or hypertrophy which is indicated by increase in size and weight at autopsy. Increase in size as shown roentgenologically indicates dilation, while increase in weight represents hypertrophy. The two conditions, however, are regularly associated. The enlargement mentioned in this paper is that observed at autopsy and is due to hypertrophy (increase in weight).

TABLE VIII

CARDIAC ENLARGEMENT (HYPERTROPHY) IN CASES OF CORONARY SCLEROSIS (923 CASES)

GRAMS	WITH HYPERTENSION (414)		WITHOUT HYPERTENSION (509)	
	MALES	FEMALES	MALES	FEMALES
250-299	0	3}	23	5}
300-349	6}	10}	82	24}
350-399	9} 3.6%	15	151	22
400-499	16	14	125	20
450-499*	19	46	57	
500 or more	276			
Total	326	88	438	71

*450, or more, for females.

Cardiac hypertrophy, as indicated by a weight of 400 gm., or more, in males, and 350 gm., or more, in females, was noted in all but twenty-eight of the 414 cases (93.2 per cent) in the hypertensive group (Table VIII). An increase in heart weight was not so common in the nonhypertensive group; 224 of the 509 (44 per cent) showed hypertrophy. In the total of 923 cases hypertrophy was noted in 610 (66 per cent); 34 per cent of the entire group showed no hypertrophy. All had severe coronary sclerosis. A causal relationship between coronary sclerosis and hyper-

trophy is not supported. It seems more reasonable to believe that the hypertrophy was due to hypertension, which was noted with practically the same frequency as the hypertrophy.

Two theories have been advanced to support the belief that cardiac hypertrophy may be due to coronary sclerosis: (1) compensatory hypertrophy of heart muscle following myocardial fibrosis, and (2) hypertrophy due to ischemia of the heart muscle.

TABLE IX

DEGREE OF MYOCARDIAL FIBROSIS ASSOCIATED WITH CORONARY SCLEROSIS (37 CASES)

	CORONARY SCLEROSIS		MYOCARDIAL FIBROSIS	
	37	100%	18	48.5%
Severe	—	—	17	46
Slight	—	—	2	5.5
Absent	—	—		

The compensatory hypertrophy theory, while seeming to have some reasonable basis, is not borne out by microscopic findings in the myocardium in cases of coronary sclerosis (Table IX). Thirty-seven hearts were examined. Severe coronary sclerosis was present in all and there was also cardiac hypertrophy in all, but myocardial fibrosis of a severe degree was present in only 48.5 per cent of the cases. Such fibrosis is just as common in hearts which are the seat of coronary sclerosis but are not hypertrophied.

TABLE X

DEGREE OF CARDIAC HYPERTROPHY IN SYPHILITIC HEARTS IN CASES IN WHICH DEATH WAS DUE TO NARROWING OF THE CORONARY ORIFICES

	SEX	MARGINAL THICKENING OF CUSPS	SEPARATION OF COMMISSURES	WEIGHT OF HEART (GM.)
1	F	—	—	275
2	F	—	—	280
3	M	—	—	305
4	F	+	+	315
5	M	+	+	350
6	M	+	+	360
7	M	—	—	360
8	F	—	—	375
9	F	—	—	385
10	M	—	—	395
11	M	—	—	395
12	M	—	—	400
13	M	—	—	415
14	M	—	—	435
15	M	+	+	600

If cardiac ischemia can cause hypertrophy it should be present in cases of syphilitic aortitis with narrowing of the coronary orifices without syphilitic valvulitis. Table X shows fifteen cases in which death was due to syphilitic narrowing of the coronary orifices. Hypertrophy to any marked extent was present in only one, and in this case the hypertrophy could be accounted for by aortic insufficiency resulting from separation

of the commissures or from free marginal thickening of the aortic cusps. Both conditions were present in this case.

Autopsy findings, gross or microscopie, offer little or no support to the theory that cardiac hypertrophy is a result of coronary sclerosis. The hypertrophy which is commonly associated with coronary sclerosis is most likely due to a coexisting primary hypertension which, as shown above, is probably present in 69 per cent of the cases of coronary sclerosis.

Infarction of the myocardium was seen in 30.5 per cent of 919 of our cases (Table XI). This was less common than thrombosis. Some patients with coronary thrombosis do not live long enough to develop gross anatomic evidence of infarction. The infarction occurred with thrombosis in 23.5 per cent of the cases and without thrombosis in 7 per cent. It is highly possible that some of the thrombi may have been missed by the pathologists, but infarcts do occur at times without a coronary thrombus. This is seen occasionally in cases with syphilitic aortitis with narrowing of the coronary orifices. As was seen with coronary thrombosis, infarction was nearly twice as common in the hypertensive group (40 per cent) as in the nonhypertensive group (22 per cent).

TABLE XI

	WITH HYPERTENSION		WITHOUT HYPERTENSION		TOTAL	
<i>Frequency of Infarction With Coronary Sclerosis (919 Cases)</i>						
With thrombus	135	32%	82	16%	217	23.5%
Without thrombus	34	8	30	6	64	7
	169	40	112	22	281	30.5
<i>Frequency of Rupture of the Heart With Coronary Sclerosis (919 Cases)</i>						
	20	5%	25	5%	46	5%

Rupture of the myocardium, with hemo-pericardium, was observed in 5 per cent of 919 cases examined (Table XI). It was usually associated with a thrombus. Sometimes there was rupture of a coronary branch, but generally the rupture was due to a softened infarct.

With myocardial infarction, if the patient lived for a few hours, or more, a mural thrombus developed, generally in the wall of the left ventricle, but sometimes in the right ventricular wall, or both. Embolic phenomena were common. Paralysis or symptoms of infarction of the lung were common early complaints of the patients.

Gross or microscopie areas of fibrosis are not infrequently seen in the myocardium in cases of death from coronary disease. This fibrosis is irregular in distribution. It appears to be due to a slow replacement of muscular tissue by connective tissue. The areas of fibrosis are not located immediately around blood vessels, as are the scars due to rheumatic inflammation. The myocardium was carefully studied microscopically in thirty-seven cases in which death was caused by coronary disease. In no case was there an infarct. Severe coronary sclerosis was present in all (Table IX). Severe myocardial fibrosis was seen in 48.5 per cent, slight

fibrosis in 46 per cent, and none in 5.5 per cent. The impression was gained that, except for rupture of the myocardium and some large infarcts, the anatomic changes observed in the myocardium in cases of coronary sclerosis are not sufficient to be the cause of death. The pathologist has not been able to find the final cause of death.

Pericardium.—Infectious pericarditis was not found in any of our cases. A fibrinous exudate regularly developed on the epicardium over recent infarcts. If the patient lived, these fibrinous exudates organized and resulted in a localized area of fibrous adhesions between the two layers of the pericardium.

Other Pathologic Findings.—The chief associated pathologic conditions observed were evidences of congestive cardiac failure, which was indicated by edema or chronic passive congestion of the liver.

The presence of edema was determined by the occurrence of anasarca, hydrothorax, or ascites (Table XII). Sufficient histories or pathologic descriptions were given in 919 cases to determine the presence or absence of edema. In the 410 patients with hypertension, edema was noted in 52 per cent. Edema was seen in only 21.5 per cent of the 509 patients without hypertension. In the total of 919, edema was observed in 35 per cent. It was more than twice as common in the hypertensive group.

TABLE XII

FREQUENCY OF EDEMA (ANASARCA, HYDROTHORAX, ASCITES) WITH CORONARY SCLEROSIS (919 CASES)

EDEMA	WITH HYPERTENSION		WITHOUT HYPERTENSION		TOTAL	
Present	213	52%	110	21.5%	323	35%
Absent	197	48	399	78.5	596	65
Total	410	100	509	100	919	100

Nine hundred nine (909) cases could be evaluated in respect to the existence of chronic passive congestion of the liver (Table XIII). Chronic passive congestion was evident in 55 per cent of the hypertensive group and in 23 per cent of the nonhypertensive group. Of the entire group of 909 cases, chronic passive congestion of the liver was present in 37.5 per cent. As with edema, chronic passive congestion of the liver was more than twice as frequent in the hypertensive group as in the nonhypertensive group.

TABLE XIII

FREQUENCY OF CHRONIC PASSIVE CONGESTION OF THE LIVER WITH CORONARY SCLEROSIS (909 CASES)

PASSIVE CONGESTION	WITH HYPERTENSION		WITHOUT HYPERTENSION		TOTAL	
Present	225	55%	116	23%	341	37.5%
Absent	185	45	383	77	568	62.5
Total	410	100	499	100	909	100

SUMMARY

Nine hundred twenty-eight (928) cases of coronary sclerosis were studied. Deaths resulting from coronary sclerosis represented about one-fourth of all deaths from noncongenital cardiac disease, or about 4 per cent of all deaths in patients above 6 months of age, in the autopsy material in the Department of Pathology at the University of Minnesota from 1910 to 1936, inclusive.

Nothing definite can be said concerning the primary cause of the disease. Death occurred most frequently in the fifth, sixth, seventh, and eighth decades, but it may take place early in the third decade. Death from coronary sclerosis was about two and one-half times as common in males as in females. Hypertension was the most common condition associated with coronary sclerosis. The great frequency suggested a causal relation.

Sudden death or death following symptoms of but a few minutes' duration was common (28 per cent). Such deaths were more common in the patients without hypertension than in those with hypertension. In patients with symptoms lasting one to five years, or more, hypertension was more common.

Pain was the most common complaint, being present in more than half of the cases. The location and variety of the pain had a marked variation. Dyspnea was the next most common symptom. Fainting, dizziness, and paralysis were not uncommon.

Effort was not a conspicuous factor in the death of these patients (10 per cent). At least 75 per cent died while at rest in the hospital or elsewhere.

The left coronary artery, especially the anterior descending branch, was the one most frequently involved. Severe right coronary involvement without a relatively severe affection of the left coronary artery rarely caused death.

Thrombosis of the arteries was present in nearly half the cases (45 per cent), 32.5 per cent in the left alone, 10 per cent in the right alone, and 3 per cent in both arteries. Thrombosis was more common in the patients with hypertension than in those without hypertension.

Hypertrophy was more than twice as common in the hypertensive as in the nonhypertensive group. There was no evidence to support the claim that cardiac hypertrophy results from coronary sclerosis. On the other hand, the hypertrophy appeared to be the result of essential hypertension.

Infarction of the myocardium was noted in 30.5 per cent of the entire group but was more frequent among the cases of hypertension. In most cases the infarction was preceded by thrombosis. Rupture of the myocardium was relatively rare (5 per cent). Some myocardial fibrosis was observed in nearly all of the hearts examined, severe in 48.5 per cent, slight in 46 per cent, and absent in 5.5 per cent.

Pericardial fibrous adhesions were noted, as a rule, only about infarcted areas.

Edema and chronic passive congestion of the liver were frequently present, but more commonly in the hypertensive group.

Excepting thrombosis, infarction, and rupture of the myocardium, the anatomic changes noted did not appear to be sufficient to be the final cause of death. In more than half of the cases, something not manifested anatomically had to be assumed to be the cause of death.

CONCLUSIONS

1. Coronary sclerosis of the atherosclerotic type, with or without thrombosis and infarction, is the most common cause of cardiac sudden death.

2. Pain is the most frequent symptom.

3. Most patients die while at rest, and only a relatively small number during effort.

4. Hypertension is the outstanding suggested etiologic factor.

5. Males predominate over females in the ratio of 2.5 to 1.

6. The disease is primarily one of adults but may be seen in younger people.

7. The incidence and degree of sclerosis are much greater in the left coronary artery than in the right.

8. Besides sclerosis of the arteries (100 per cent), the chief anatomic changes noted are thrombosis (45 per cent), hypertrophy (66 per cent), infarction (30.5 per cent), rupture of myocardium (5 per cent), and myocardial fibrosis (severe, 48.5 per cent; slight, 46 per cent; and none, 5.5 per cent).

9. Edema was noted in 35 per cent of the cases, more frequently in the hypertensive group. Chronic passive congestion of the liver was seen with about the same frequency in the two groups.

10. In more than half the cases an anatomic change considered sufficient to cause death was not evident.

REFERENCES

1. Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, 1936, The Macmillan Company.
2. White, Paul D.: Heart Disease, New York, 1937, The Macmillan Company.
3. Dublin, L. I.: Statistics of Diseases of the Coronary Arteries (Reference 1, p. 183).
4. Bell, E. T., and Clawson, B. J.: Primary (Essential) Hypertension, Arch. Path. 5: 939, 1928.

BLOOD OXYGEN CHANGES FOLLOWING INTERMITTENT VENOUS OCCLUSION*

J. ROSS VEAL, M.D., WASHINGTON, D. C., AND
WILLIAM MELLEN McCORD, PH.D., NEW ORLEANS, LA.

THE most important investigation of reactive hyperemia which has been made to date is the study published by Lewis and Grant¹ in 1925, more than fifty years after Cohnheim first described the phenomenon and more than twenty-five years after Bier applied its present name to it and suggested a possible therapeutic application for it. The conclusions of Lewis and Grant, which were arrived at by direct visual observation and by volumetric studies with the plethysmograph, are substantially as follows:

1. Occlusion followed by release of the arterial supply of an extremity brings about a degree of vasodilatation which is proportionate to the duration of the occlusion, within certain limits; generally speaking, an occlusion of five seconds is necessary to produce any perceptible reaction, and the reaction lasts a half to three-quarters as long as does the previous period of circulatory arrest. The reaction is greater in a limb the temperature of which is raised, though it is unaffected by changes of external temperature.

2. The reaction affects not only the superficial vessels, as evidenced by changes in the color of the skin, but also the deeper vessels, as proved by volumetric studies and by measurement of the inflow to the limb.

3. A similar reaction occurs when venous pressure is increased. Both the degree and the duration of the reactive hyperemia increase as the congestion is raised from 40 mm. Hg, the minimum necessary to produce any perceptible reaction, and at very high venous pressures the reaction is very like that produced by arterial occlusion. Within certain time limits both the degree and the duration of the reaction are increased by the duration of the congestion.

4. The reaction is a local one and is independent of both the central nervous system and the local reflexes.

Bier's suggestion that active or passive venous congestion be employed in the treatment of pathologic states of the soft tissues has been accepted for many years, though the mechanism of its favorable action has never been satisfactorily explained. Formerly this method of treatment was applied only to diseases in which the arterial blood supply was not primarily involved, but recently, and still more or less empirically, it has been applied to conditions in which an arterial deficiency is the basic pathologic change.

*From the Departments of Surgery and Biochemistry of the School of Medicine of Louisiana State University and the State of Louisiana Charity Hospital at New Orleans.

Received for publication Sept. 10, 1938.

Collens and Wilensky² have recently applied the principle of reactive hyperemia in the treatment of peripheral vascular diseases, and have also described a simple apparatus for producing the hyperemia. In 1937, de Takáts, Hick, and Coulter³ reviewed the whole subject of reactive hyperemia and reported the use of the Collens and Wilensky technique in ten patients. In their cases, however, statements concerning its good results must be somewhat qualified, for other methods of treatment were also employed, and other factors thus introduced. It is worth mentioning that these authors issue a specific warning that the same contraindications should be observed in the use of reactive hyperemia in the treatment of peripheral vascular disease as are observed in the use of alternate suction and pressure therapy.

The underlying mechanism of the phenomenon needs much further investigation. In true reactive hyperemia there is a marked increase in the blood volume flow, as is proved by the objective color changes in the skin, which are in turn evidence of an increased amount of arterial blood in the venous system. If intermittent venous occlusion produces a true reactive hyperemia, it also should be associated with an increase in the blood volume flow, which in turn should be evidenced by a rise in the oxygen content of the venous blood. The studies of de Takáts and his associates would seem to prove the contrary. Their observations on the percentage of oxygen saturation of the blood at intervals of twenty and forty minutes after the release of intermittent venous compression fail to show any increase, but, on the contrary, show an actual decrease.

The explanation of the findings of de Takáts, et al., is not far to seek. The duration of reactive hyperemia produced by complete occlusion of the vascular system of an extremity is transitory, and it seems scarcely reasonable to expect to demonstrate blood changes much beyond the period of its existence. This present communication is a report of a study of the oxygen saturation of the blood made during the period in which the reactive hyperemia should be demonstrable.

TECHNIQUE OF EXPERIMENTS

The investigation was conducted upon eleven healthy male subjects, with normal cardiovascular systems, and the circumstances of the test were identical in each instance. Each test was preceded by a rest period of thirty to sixty minutes, during which the patient lay on a table, at room temperature, with his arms stretched beside his body at heart level. A blood pressure cuff was so adjusted on the arm to be studied that it could be instantly released. All samples of blood were collected under oil from the antecubital vein, without the use of a tourniquet, the needle being left in situ whenever successive specimens were collected. The Van Slyke⁴ method for determination of the oxygen content of the blood was used throughout.

After a control sample of blood had been collected at the conclusion of the rest period, the first test was undertaken, as follows: The arm was elevated to empty the veins, the blood pressure cuff was abruptly inflated to 250 mm. Hg, and the arm was returned to heart level. Then, at periods varying from five to eight minutes in

each subject, the cuff was deflated equally suddenly and the return of circulation permitted. Samples of blood were collected one minute and three minutes after the release of the occlusion.

In the second test the blood pressure cuff was inflated with the arm at heart level, and intermittent venous occlusion was instituted over periods ranging from fifteen to sixty minutes. In all cases the duration of the compression was a period of two minutes, but the interval of release was variously one minute and two minutes. The range of pressure was from 60 to 80 mm. Hg. Specimens of blood were withdrawn, as in the first test, one minute and three minutes after the final release of the occlusion.

RESULTS

The percentage of the oxygen saturation of the blood after complete vascular compression and after intermittent venous occlusion, as compared with the percentages in the resting period, are shown in Tables I and II, the findings of which may be briefly summarized.

TABLE I

OXYGEN CHANGES IN VENOUS BLOOD AFTER RELEASE FROM COMPLETE VASCULAR OCCLUSION

CASE NUMBER	PERCENTAGE OF OXYGEN SATURATION RESTING STATE	PERCENTAGE OF OXYGEN SATURATION 1 MIN. AFTER RELEASE	PERCENTAGE OF OXYGEN SATURATION 3 MIN. AFTER RELEASE
1.	62	77	91
2.	86	70	86
3.	61	77	
4.	63	69	58
5.	66	88	93
6.	78	97	84
7.	53	90	85
8.	81	95	81
9.	75	75	66
10.	60	90	89
11.	85	96	94

After complete arterial occlusion for five to eight minutes (Table I) there was a definite rise in the oxygen saturation of the blood from the antecubital vein in nine of the eleven cases studied at the end of one minute after the pressure was released; in one case the percentage was unaltered, and in another there was a fall of sixteen points. At the end of three minutes the oxygen-saturation percentage was still increased over the resting period in six of ten cases; in two cases the percentage was unchanged, and in two there was a slight fall. In some individuals the return to normal levels was rapid, in others the elevation tended to persist, but the general tendency of the whole group was toward an increase in the oxygen saturation of the blood.

After intermittent venous occlusion, however, the tendency was exactly reversed. In eight of the eleven cases (Table II) there was a definite decrease in the oxygen saturation of the blood at the end of one minute after the release of the compression, and an increase in only three cases.

The tendency was less clearly defined at the end of three minutes; in eight cases studied at that time there was a decrease of the oxygen saturation in four, a very definite elevation in two, and in two others an elevation of one and three points, respectively, which can probably be disregarded, as a 5 per cent variation must be allowed as within the range of normal laboratory error.

TABLE II

OXYGEN CHANGES IN VENOUS BLOOD AFTER INTERMITTENT VENOUS OCCLUSION

PERIOD OF TEST	CASE NUMBER	PERCENTAGE OF OXYGEN SATURATION RESTING STATE	PERCENTAGE OXYGEN SATURATION 1 MIN. AFTER RELEASE	PERCENTAGE OF OXYGEN SATURATION 3 MIN. AFTER RELEASE
15 minutes	1.	62	55	
18 minutes	2.	61	46	50
30 minutes	3.	80	75	75
30 minutes	4.	73	50	58
30 minutes	5.	66	55	85
45 minutes	6.	78	68	81
45 minutes	7.	56	68	
45 minutes	8.	85	81	
1 hour	9.	75	69	67
1 hour	10.	60	61	62
1 hour	11.	82	92	88

SUMMARY

The results of this study would seem to indicate that complete vascular occlusion in the presence of a normal circulatory system is followed by a true reactive hyperemia immediately upon release of the compression. The maintenance of complete compression over periods of five to eight minutes was generally followed by a definite rise in the oxygen saturation of the venous blood one minute after its release, and in most cases the elevation was maintained at the end of three minutes. It may therefore be assumed that the reactive hyperemia produced by this type of occlusion brings about a more rapid flow of blood through the extremity, as well as a marked increase in the volume of the flow.

Intermittent venous occlusion, on the other hand, even in the presence of a normal circulatory system, is usually followed by a lowering of the oxygen saturation of the venous blood at one minute as well as three minutes after the release of the occlusion. This would seem to indicate that under the circumstances of this test (with a pressure varying from 60 to 80 mm. Hg, and with a ratio of compression and release of 2:2 and 2:1) a true reactive hyperemia is not produced. Any favorable effects claimed for this type of therapy must therefore result not so much from an increase in the rate or the volume of the blood flow as from some chemical changes produced in the tissues incident to the venous congestion and the changes produced by the increased venous pressure.

It might be said in conclusion that these findings bear out those of Allen and McKechnie⁵ in their study of the effect of intermittent venous occlusion on the skin temperature under controlled circumstances. In nineteen patients (nine normal subjects, and ten with hypertension, arthritis, and peripheral vascular disease) they found no evidence that any significant or consistent vasodilatation resulted from the procedure.

REFERENCES

1. Lewis, T., and Grant, R. T.: Observations on Reactive Hyperemia in Man, *Heart* 12: 73, 1925.
2. Collens, W. S., and Wilensky, N. D.: The Use of Intermittent Venous Compression in the Treatment of Peripheral Vascular Disease, *AM. HEART J.* 11: 705, 1936; An Apparatus for the Production of Intermittent Venous Compression in the Treatment of Peripheral Vascular Disease, *AM. HEART J.* 11: 721, 1936.
3. De Takáts, G., Hick, F. K., and Coulter, J. S.: Intermittent Venous Hyperemia in the Treatment of Peripheral Vascular Disease, *J. A. M. A.* 108: 1951, 1937.
4. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Vol. 2, Baltimore, 1932, Williams & Wilkins Company.
5. Allen, E. V., and McKechnie, R. E.: Effect of Intermittent Venous Occlusion on the Circulation of the Extremities, *J. Lab. & Clin. Med.* 22: 1260, 1937.

THE NORMAL HEART VOLUME IN MAN

G. LILJESTRAND, E. LYSHOLM, G. NYLIN, AND C. G. ZACHRISSON
STOCKHOLM, SWEDEN

WHEN trying to determine the size of the heart in the living subject reliance has usually been placed mainly on the values established from measurements on the frontal orthodiagrams alone. Though the results thus obtained have sometimes been of importance—e.g., for comparative studies of the heart on different occasions—the practical use of the method has been greatly hampered by the fact that the heart volume cannot be determined in this way with a sufficient degree of accuracy. The main objection is, of course, that frontal orthodiagrams alone can be employed for this purpose only if the form of the heart is the same not only in one individual under different conditions, but also in different individuals. As is well known, this is far from being the case (see below), great variations often occurring in the form of the heart. Under these circumstances it has been found necessary to try to arrive at more exact methods for establishing the heart volume. Thus Palmieri¹ (1920), Lysholm² (1926), and Wegelius³ (1934) made models of the heart with the aid of projections in several planes. This modeling procedure, however, takes a long time and will therefore hardly be of practical importance. It was a great advance in this field when it was shown independently by Rohrer⁴ (1916-1917) and Kahlstorf⁵ (1932) that it is possible to calculate the volume of the heart with satisfactory accuracy from the frontal and sagittal orthodiagrams. They assumed that the heart is of a shape between a paraboloid and an ellipsoid. The size of the heart can then be calculated according to the formula $V = 0.63 \cdot F_a \cdot L_{max}$, where V is the volume of the heart, F_a the area of sagittal orthodiagram, and L_{max} the maximum depth of the transversal orthodiagram. The reliability of this calculation was demonstrated by Kahlstorf, who investigated nine normal and three pathologic hearts from corpses. The hearts had been hardened in formalin and were mounted on a stand; orthodiagrams were made in two directions at right angles. Each preparation was investigated in three different positions, and the values obtained were compared with the volume as found by water displacement. The agreement was very good, the difference between the calculated and observed volumes being not more than ± 5 per cent. The method was applied to determinations of the normal heart volume in living persons by Rohrer in seven cases. In five of these the values lay between 471 and 575 c.c.; in one, obviously a very small individual (height 140 cm.), it was only

From medical clinic 11 and the roentgenologic department of the Serafimer Hospital and the department of pharmacology of the Karolinska Institute, Stockholm.

Received for publication Sept. 3, 1938.

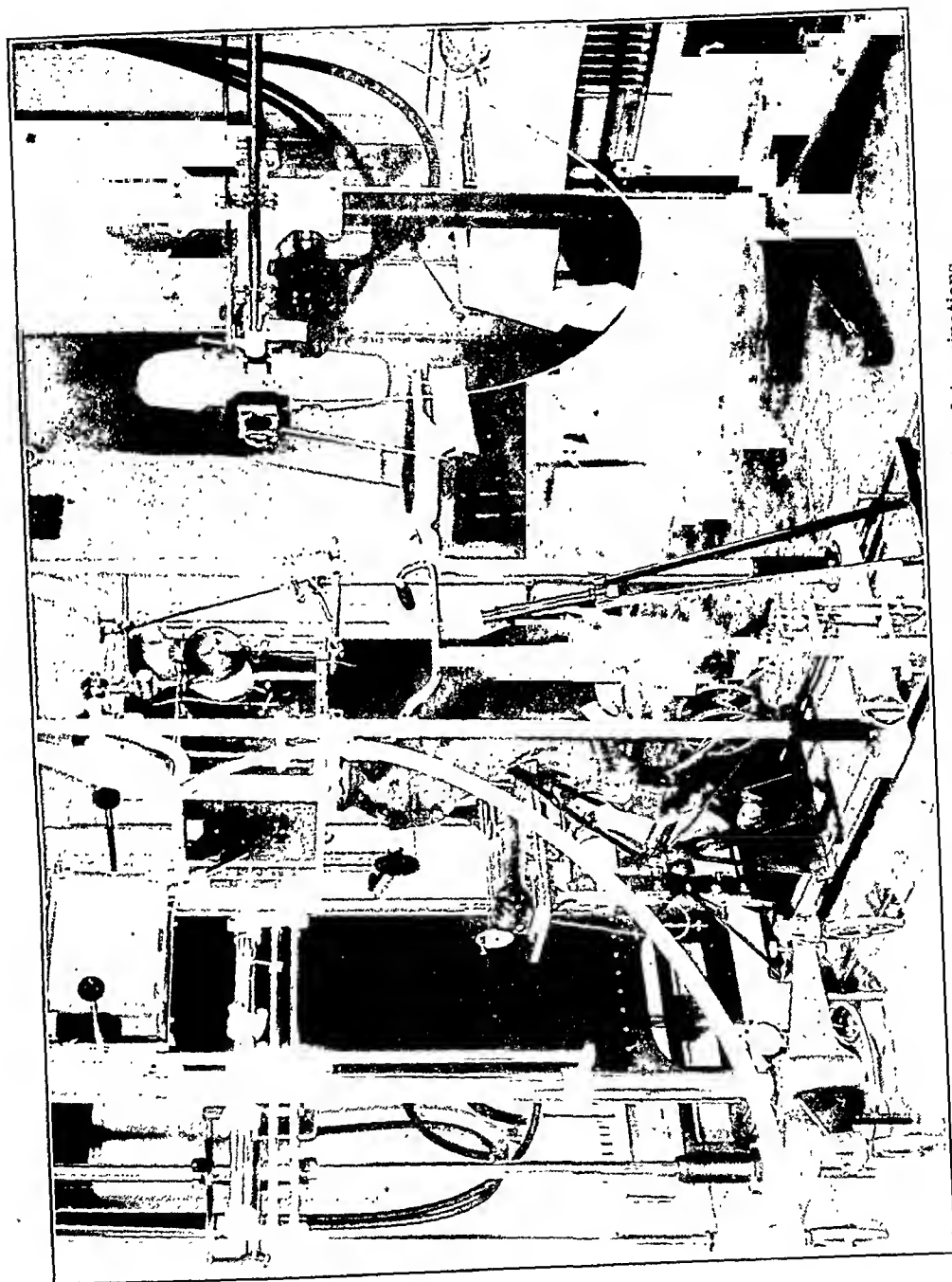


Fig. 1.—General arrangement of the apparatus for the determinations.

216 c.c.; and in the remaining subject (height 170 cm.) 762 c.c. Kahlstorf has examined a much larger group, comprising seventy men and fifty women. All of his determinations were made with the subject in the standing position, a fact of some importance, since it is known that the heart is considerably larger when the subjects are in the recumbent than when they are in the erect position (cf. Nylin,⁶ 1934). Kahlstorf calculates his values in relation to the body weight (he finds a direct proportion between them) and arrives at the conclusion that the heart volume per kg. of body weight is at least 7 c.c. in female and 8 c.c. in male subjects, and that it does not exceed 11 c.c. For the erect position Lysholm, Nylin, and Qvarnå⁷ (1934) have determined the heart volume in thirty-three normal male subjects according to the Rohrer-Kahlstorf formula. The average was 627 ± 22 c.c., the extreme limits observed being 393 and 860 c.c.. As far as can be judged, their values agree well with those of Kahlstorf.

The following investigation on the normal heart volume was carried out on a larger number of subjects; they were young students, 20 to 30 years of age, and bank clerks between the ages of 37 and 47 years, all of whom were in perfect health and exhibited no signs of heart or vascular disease.

For our determinations the devices for biplane radiography were constructed around a Krogh ergometer bicycle and manufactured in the shops of Mr. G. Schönander in 1935 (Fig. 1). In front of and at the side of the subject were placed two films at right angles. Corresponding to these were two 40 kw. roentgen tubes with rotating anodes, mounted on special stands and placed at a distance of 1.5 and 2 M. from the films. The high tension was adjusted to 90 kv. peak, the tubes being coupled in parallel. The milliamperage was so regulated that the tube corresponding to the side view had a load of 250 Ma., and the other tube 200 Ma. The high tension switches (*s* in Fig. 2) enabled us to use each tube separately or both simultaneously. The arrangement was constructed in the autumn of 1935 by the firm of Siemens Reiniger Veifa, in Stockholm, and has since worked satisfactorily. During the exposure, the front and the side of the chest were gently pressed against the two cassette-holders. The exposure time was one-twentieth second. To cut off scattered radiation during simultaneous exposures, two crossed Lysholm all-metal grids were used in each of the two planes. This arrangement satisfactorily eliminates the scattered radiation and prevents blurring in the roentgenogram.

For the calculation of the heart volume, it is necessary to introduce a correction for the enlargement of the heart shadow on the film. Fig. 3 illustrates this. Assuming the heart to be an ellipsoid, one gets the volume *V* from the equation:

$$V = \frac{4\pi}{3} \cdot \frac{200-a}{200} \cdot \frac{1}{2} \cdot \frac{200-a}{200} \cdot \frac{m}{2} \cdot \frac{150-b}{150} \cdot \frac{n}{2}$$
, where *l* and *m* are the axes of the ellipsoid on the frontal and *n* the axis on the lateral view, and *a* and *b* the distances from the center of the heart to the films. Direct measurements gave for *a* and *b*, 15 and 23 cm., respectively, so that the formula is reduced to $V = 0.38 \cdot l \cdot m \cdot n$.

We have thus assumed the heart to have the form of an ellipsoid, whereas the Rohrer-Kahlstorf formula takes it to be something between

a paraboloid and an ellipsoid. Thus they get the constant 0.63, whereas here it is 0.67. Our values will therefore be 6 per cent higher than those of Rohrer and Kahlstorf.

In order to determine the margin of error for the method, we have made double exposures on ten healthy medical students. The values obtained are given in Table I. We find the margin of error as small as 30 c.e., corresponding to 4.7 per cent of the mean value.

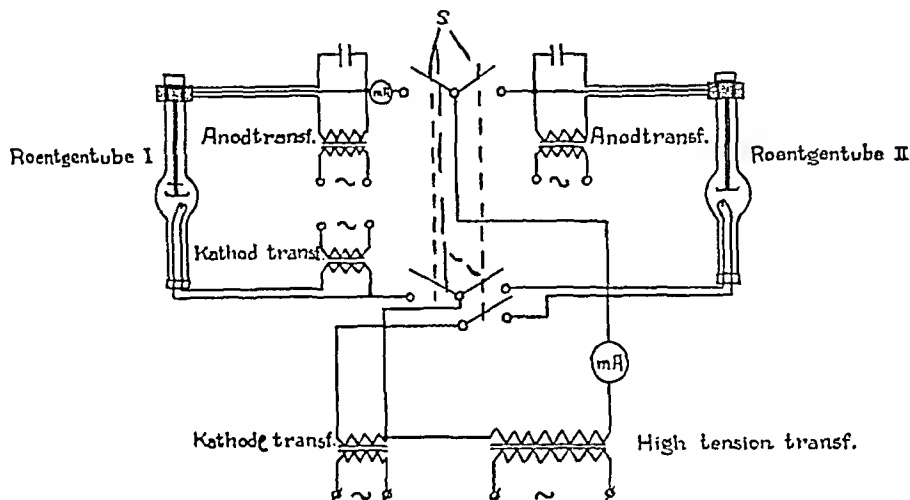


Fig. 2.—Arrangement of roentgen tubes (s, switches).

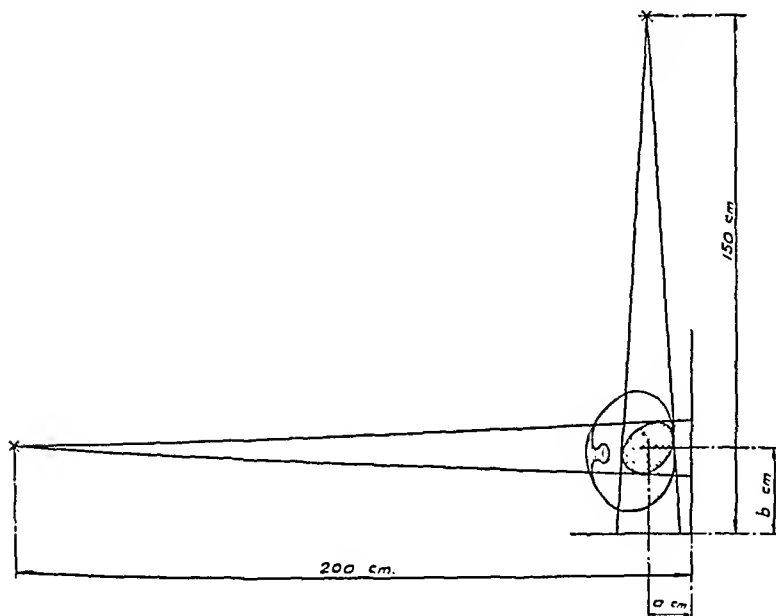


Fig. 3.—Scheme for correction.

Before giving the details of our observations we should like to exemplify by means of two cases the paramount importance of taking into consideration two projections in different planes for the estimation of the heart volume. Fig. 4 shows the frontal and sagittal teleroentgeno-

grams of a healthy nurse in a sitting position. On the frontal projection the heart looks enlarged, but the sagittal diameter is exceedingly short. The subject had a very flat chest. Calculating the heart volume according to the Rohrer-Kahlstorf formula, we get the normal value of 900 c.e., or 450 c.e./m² of body surface. On the other hand, if the heart volume is calculated only on the basis of the frontal roentgenogram with the help of Bardeen's⁵ formula (1918), it amounts to 1,300 c.e., which is 45 per cent higher than the value obtained by the method first mentioned. Fig. 5 illustrates the reverse situation in another normal subject, also in a sitting position. Here the heart is tubular, as shown by the frontal roentgenogram, but the chest is deep, and the sagittal diameter fairly large. The heart volume according to Bardeen's formula is 400 c.e., but by the Rohrer-Kahlstorf method we obtain 490 c.e.; thus with the former the estimate is 23 per cent too small.

TABLE I

TWO DETERMINATIONS OF HEART VOLUME ON EACH OF TEN NORMAL STUDENTS

SUBJECT	NO.	LENGTH CM.	BREADTH CM.	SAGITTAL DIAMETER CM.	HEART VOLUME C.C.	DIFFERENCE C.C.
1.	I	14	11.5	9.5	580	0
	II	14	11.5	9.5	580	
2.	I	14.5	10.5	12	690	25
	II	14.5	10.5	11.5	665	
3.	I	13	11	11	600	50
	II	12	10.5	11.5	550	
4.	I	15.5	12	10	710	50
	II	15	11.5	10	660	
5.	I	13.5	11.5	9.5	560	65
	II	13	10.5	9.5	495	
6.	I	15	12	10	690	0
	II	15	12	10	690	
7.	I	14.5	12	9.5	630	0
	II	14.5	12	9.5	630	
8.	I	15	11.5	12	700	65
	II	15	11	12	755	
9.	I	12.5	10.5	12	600	50
	II	13	11	12	650	
10.	I	14.5	12	10	660	30
	II	14.5	12	9.5	630	

General mean = 641 c.c. Mean of differences irrespective of signs = 34 c.c.
Margin of the error for the method = 30 c.c. = 4.7 per cent of the mean value.

The results of our determinations on healthy men are given in Tables II and III. In the first group of seventy medical students (Table II) the absolute volume of the heart varies between 480 and 970 c.e., which is considerable. The corresponding limits are 5.6 and 14.2 c.e. per kilogram of body weight. The subject with the lower limit (No. 69) stands out as an exception, since in all the other subjects the heart exceeds 7.8 (corrected 7.4) c.e. per kilogram, which is in fairly good agreement with Kahlstorf's experiences. In seven cases, however, the values are higher than the upper limit given by Kahlstorf ($11 \cdot 106 = 11.7$ c.e.). In our

smaller group of men from 32 to 47 years of age, all are at or above eight (7.5 corrected) c.c. per kilogram, but here also some subjects, in all three, have a volume larger than 11.7 c.c. per kilogram. We are thus led to the conclusion that the upper limit for the size of the normal heart is somewhat higher than given by Kahlstorf.

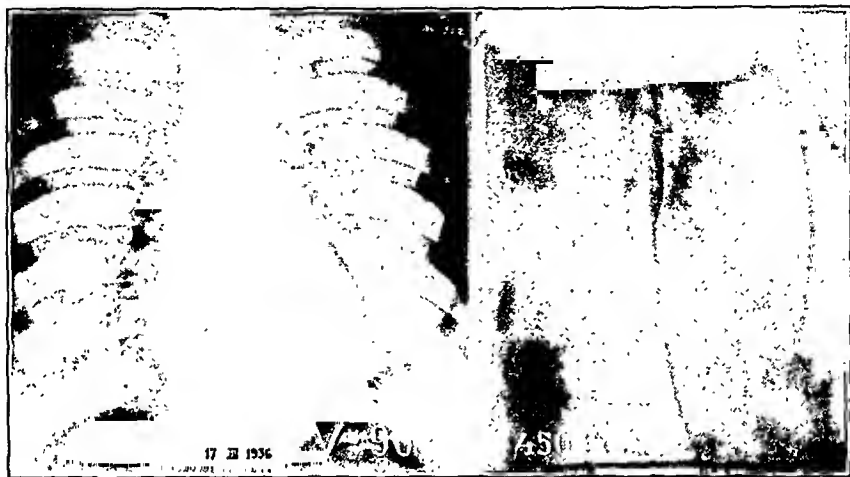


Fig. 4.—Heart volume in a healthy nurse with extremely flat chest.

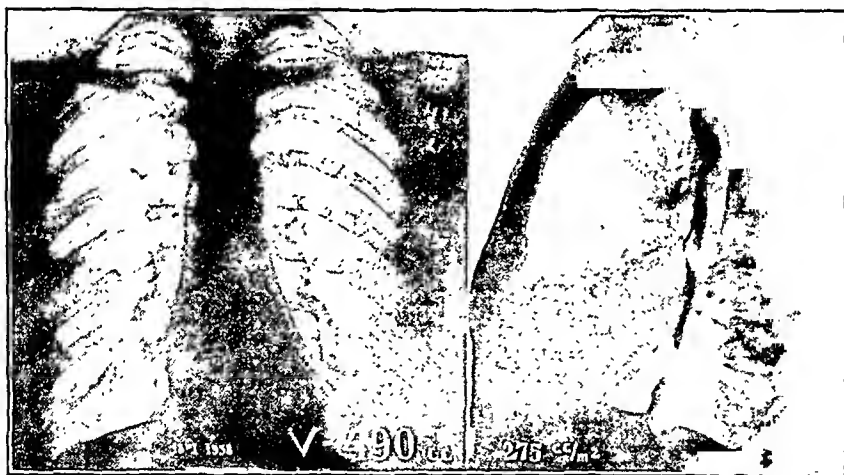


Fig. 5.—Heart volume in a healthy girl with a deep chest.

Since it has been observed in previous investigations (cf. DuBois,⁹ 1936, and Grollman,¹⁰ 1932) that metabolism and blood flow show a closer correlation to the body surface than to the body weight, it would seem natural also to correlate the heart volume with the body surface. Fig. 6 demonstrates the excellent correlation obtained in this way.

On the basis of the above-mentioned determinations, we have worked out our material statistically. The calculation of mean values and standard deviations has been made in accordance with well-known formulas.

TABLE II

HEART VOLUME OF SEVENTY HEALTHY MEDICAL STUDENTS BETWEEN 21 AND 30
YEARS OF AGE

NO.	AGE YEARS	HEIGHT CM.	WEIGHT KG.	BODY SUR- FACE M ²	HEART VOLUME C.C.	HEART VOLUME C.C. PER M ²	HEART VOLUME C.C. PER KG.
1.	21	175	68	1.82	530	290	7.8
2.	21	160	57	1.58	620	390	10.9
3.	22	193	91	2.22	850	380	9.3
4.	22	173	58	1.70	650	380	11.2
5.	22	177	73	1.89	850	450	11.6
6.	22	184	66	1.87	650	350	9.8
7.	22	190	86	2.14	850	400	9.9
8.	22	176	63	1.77	650	370	10.3
9.	22	176	62	1.76	680	390	11.0
10.	22	190	78	2.06	710	350	9.1
11.	22	184	81	2.04	660	320	8.1
12.	22	179	62	1.77	600	340	9.7
13.	22	172	65	1.77	830	470	12.8
14.	22	171	61	1.72	750	440	12.3
15.	22	174	64	1.77	830	470	13.0
16.	22	185	83	2.07	800	390	9.6
17.	22	168	68	1.78	660	370	9.7
18.	23	205	78	2.20	900	410	11.5
19.	23	170	66	1.77	700	400	10.6
20.	23	177	72	1.87	730	390	10.1
21.	23	184	67	1.87	550	290	8.2
22.	23	175	62	1.76	550	310	8.9
23.	23	181	76	1.96	600	310	7.9
24.	23	180	65	1.83	520	280	8.0
25.	23	176	67	1.81	750	410	11.2
26.	23	181	68	1.78	800	450	11.7
27.	23	172	66	1.78	520	290	7.9
28.	23	184	75	1.97	600	310	8.0
29.	23	176	60	1.74	480	280	8.0
30.	23	183	78	2.01	750	370	9.6
31.	23	182	69	1.68	650	390	9.4
32.	23	168	65	1.74	590	340	9.1
33.	24	180	77	1.96	850	430	11.0
34.	24	184	78	2.01	750	370	9.6
35.	24	182	71	1.92	680	350	9.6
36.	24	186	79	2.02	900	450	11.4
37.	24	180	77	1.96	830	420	10.7
38.	24	182	63	1.83	520	280	8.3
39.	24	172	69	1.81	800	440	11.6
40.	24	179	65	1.82	750	410	11.5
41.	24	169	71	1.81	750	410	10.6
42.	24	161	51	1.53	430	280	8.4
43.	24	173	65	1.78	550	310	8.5
44.	24	183	78	2.01	660	330	8.5
45.	24	181	78	1.99	650	330	8.3
46.	24	187	91	2.17	780	360	8.6
47.	24	183	78	2.01	610	300	7.8
48.	24	182	70	1.90	620	330	8.9
49.	24	170	75	1.86	580	310	7.7
50.	25	180	68	1.87	800	430	11.8
51.	25	173	76	1.91	750	390	9.9
52.	25	176	74	1.89	780	410	10.5
53.	25	175	84	1.99	970	490	11.5

TABLE II (CONT'D)

NO.	AGE YEARS	HEIGHT CM.	WEIGHT KG.	BODY SUR- FACE M ²	HEART VOLUME C.C.	HEART VOLUME C.C. PER M ²	HEART VOLUME C.C. PER KG.
54.	25	170	61	1.72	870	510	14.2
55.	25	189	75	2.01	600	300	8.0
56.	25	172	71	1.84	600	330	8.5
57.	25	175	69	1.84	550	300	8.0
58.	25	176	65	1.80	800	440	12.3
59.	25	176	67	1.82	690	380	10.3
60.	25	184	76	1.98	760	380	10.0
61.	26	186	75	1.98	830	420	11.1
62.	26	184	96	2.20	930	420	9.7
63.	26	175	65	1.79	580	320	9.0
64.	26	181	64	1.82	780	430	12.1
65.	26	176	68	1.84	730	400	10.7
66.	26	181	71	1.91	750	390	10.6
67.	27	179	75	1.94	780	400	10.4
68.	27	175	64	1.78	600	340	9.4
69.	29	183	85	2.07	480	230	5.6
70.	30	180	85	2.04	850	420	10.0

We have considered as normal limits the mean value decreased and increased by two standard deviations. The mean value for the heart volume for the 70 young students is found to be 700 c.e., and for the somewhat older men it amounts to 750 c.e. Calculated per kilogram of body weight (Table IV), the mean heart volume amounts to 9.8 c.e. for the younger group and 10.4 c.e. for the older one. The corresponding values per m² of body surface are 372 and 395 c.e., respectively. The normal limits for these 101 healthy male subjects, estimated as mentioned above, are 7.0 and 13.0 c.e. per kilogram body weight and 250 and 490 c.e. per m² of body surface.

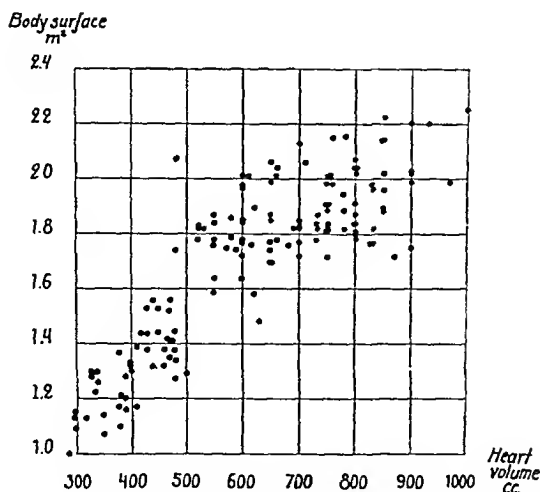


Fig. 6.—Correlation between heart volume and body surface.

TABLE III

HEART VOLUME OF THIRTY-ONE HEALTHY BANK CLERKS BETWEEN 32 AND 47
YEARS OF AGE

NO.	AGE YEARS	HEIGHT CM.	WEIGHT KG.	BODY SUR- FACE M ²	HEART VOLUME C.C.	HEART VOLUME C.C. PER M ²	HEART VOLUME C.C. PER KG.
1.	32	173	71	1.84	800	440	11.3
2.	32	182	83	2.02	800	400	9.6
3.	32	173	88	2.03	900	440	10.2
4.	33	171	66	1.78	730	410	11.1
5.	34	182	92	2.14	850	400	9.2
6.	34	172	61	1.72	600	350	9.8
7.	34	178	73	1.91	800	420	11.0
8.	34	172	69	1.82	730	400	10.6
9.	35	167	63	1.72	700	410	11.1
10.	35	168	75	1.85	650	350	8.7
11.	36	177	68	1.85	600	320	8.8
12.	36	190	72	1.98	750	380	10.4
13.	36	181	94	2.15	760	350	8.1
14.	37	181	67	1.88	750	400	11.2
15.	38	174	63	1.76	630	360	10.0
16.	38	187	80	2.06	650	320	8.1
17.	39	181	77	1.99	900	450	11.7
18.	39	178	84	2.02	850	420	10.1
19.	39	176	68	1.84	750	410	11.0
20.	39	183	64	1.85	700	380	10.9
21.	40	172	57	1.66	550	330	9.6
22.	40	175	72	1.87	800	430	11.1
23.	40	186	87	2.13	700	330	8.0
24.	40	178	67	1.88	850	450	12.7
25.	40	172	62	1.74	650	370	10.5
26.	42	176	60	1.75	575	330	9.6
27.	42	163	67	1.75	900	510	13.4
28.	42	188	78	2.04	800	390	10.3
29.	43	172	67	1.82	830	460	12.4
30.	44	173	68	1.83	700	380	10.3
31.	47	185	101	2.25	1000	440	9.9

TABLE IV

TOTAL HEART VOLUME, HEART VOLUME PER SQUARE METER OF BODY SURFACE AND
PER KILOGRAM OF BODY WEIGHT OF 101 HEALTHY MEN

		AVERAGE M C.C.	STAND- ARD DEVI- ATION σ	V	MEAN ERROR $\Sigma (M)$	M \pm 2 σ
70 medical students aged 21-30 years	Heart volume c.c.	700.7	121.9	17.4	14.6	457-945
	Heart volume c.c./m ² .	371.7	58.9	15.8	7.0	254-490
	Heart volume c.c./kg.	9.8	1.6	16.5	0.2	6.16-13.0
31 men aged 32-47 years	Heart volume c.c.	750.0	106.5	14.2	19.1	537-963
	Heart volume c.c./m ² .	394.5	45.8	11.6	8.2	303-486
	Heart volume c.c./kg.	10.4	1.3	12.4	0.2	7.8-13.6

We have not been able to establish with certainty from these investigations any pronounced difference between the age groups, even though there is a tendency toward a larger heart volume at a more advanced

age. In a previous paper, Nylin¹¹ (1935) calculated the heart volume of twelve healthy girls between twelve and fourteen years of age, and found that the mean value (standing) was 315 c.c. per m² of body surface. Comparing the results obtained for the girls and the results of this investigation (Table V), there appears to be a tendency toward an increase in the heart volume per m² of body surface with increasing age, but unfortunately the youngest group was not of the same sex as the other two groups.

TABLE V

TOTAL HEART VOLUME AND HEART VOLUME PER SQUARE METER OF BODY SURFACE AT DIFFERENT AGES

	AGE (YR.)	HEART VOLUME		
		C.C.	C.C./M ² .	M \pm 2 σ C.C./M ² .
12 girls	12-14	417	315	255-375
70 men	21-30	701	372	254-490
31 men	32-47	750	395	303-486

SUMMARY

We have determined by simultaneous roentgenograms, in two projections at right angles, values for the volume of the heart in 101 healthy men, aged from 21 to 47 years, and found that the normal heart volume varies between 7.0 and 13.0 c.c. per kilogram body weight and between 250 and 490 c.c. per m² of body surface.

REFERENCES

1. Palmieri, G. G.: Sul valore della ricerca dell' "angolo di scomparsa della punta" (metodo Vaguez-Bordet) come indice del volume relativo del cuore; variazioni di tale angolo nello stesso individuo e loro cause, *Malat. d. cuore* 4: 184, 1920.
2. Lysholm, E.: Röntgenoskopischer Modellierungsapparat auch für Quersektion und Lokalisation, *Acta radiol.* 7: 189, 1926.
3. Wegelius, C.: Untersuchungen über die Möglichkeiten einer dreidimensionalen, röntgenographischen Abgrenzung innerer Organe des menschlichen Körpers, Helsingfors, 1934.
4. Rohrer, F.: Volumbestimmung von Körperhöhlen und Organen auf orthodiagraphischem Wege. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 24: 285, 1916.
5. Kahlstorf, A.: Ueber eine orthodiagraphische Herzvolumenbestimmung, *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 45: 123, 1932.
Kahlstorf, A.: Möglichkeiten und Ergebnisse röntgenologischer Herzvolumenbestimmungen, *Klin. Wchnschr.* 17: 223, 1938.
6. Nylin, G.: Relation Between Heart Volume and Stroke Volume in Recumbent and Erect Positions, *Skandinav. Arch. f. Physiol.* 69: 237, 1934.
7. Lysholm, E., Nylin, G., and Quarnä, K.: The Relation Between the Heart Volume and Stroke Volume Under Physiological and Pathological Conditions, *Acta radiol.* 15: 237, 1934.
8. Bardeen, C. R.: Determination of the Size of the Heart by Means of the X-Rays, *Am. J. Anat.* 23: 423, 1918.
9. DuBois, E. F.: *Basal Metabolism in Health and Disease*, Ed. 3. Philadelphia, 1936, Lea & Febiger.
10. Grollman, A.: *The Cardiac Output of Man in Health and Disease*, Springfield, 1932, Charles C. Thomas.
11. Nylin, G.: *The Physiology of the Circulation During Puberty*, *Acta med. Scandinav. Suppl.* 69, 1935.

FOLLOW-UP STUDY OF SYSTOLIC MURMURS*

M. J. SHAPIRO, M.D.

MINNEAPOLIS, MINN.

THE systolic murmur, which had so long been considered insignificant, has again gained a position of importance. Those of us who examined the "command for cardiovascular disease" during the last war can remember that we were instructed to disregard the systolic murmur. It was the accepted teaching during that period that so-called functional or nonpathologic murmurs were common in normal, healthy individuals. It was taught that mitral regurgitation rarely occurred without stenosis and that the systolic murmur alone did not mean mitral disease. Some believed that the use of the stethoscope had done more harm than good. This was in contrast to the point of view held in the period just after the discovery of the stethoscope. At that time, every murmur in the heart was considered indicative of organic heart disease. Systolic murmurs at the apex were believed to be diagnostic of mitral regurgitation. In the past few years, however, the pendulum has made another wide sweep in the opposite direction and we are now advised that almost every systolic murmur is of significance and needs to be carefully studied; that while nonpathologic murmurs do exist, they are much fewer in number than formerly believed. We are told that, by careful physical examination, it will be found that most of these murmurs mean either organic heart disease or are indicative of heart abnormalities secondary to such conditions as anemia, hyperthyroidism, or hypertension.¹ The two most recent reports on the systolic murmur, by White² and Levine,¹ were based on a single examination of a large number of individuals with no follow-up study.

At the Lymanhurst Heart Clinic we have been able to carry on a follow-up study on 102 patients on whom an original diagnosis of nonpathologic murmur was made. The initial examination as well as all subsequent follow-up examinations were made by the writer. This is a select group, in that every effort was made to exclude all patients with possible early organic heart disease. The criteria for making a diagnosis of nonpathologic murmur were as follows: (1) No history of rheumatic infection; (2) murmur in the heart not characteristic of congenital heart disease; (3) heart normal in size and contour, as shown by postero-anterior and lateral roentgenograms and by fluoroscopy when indicated; (4) no evidence of anemia or hyperthyroidism.

Patients who gave a history of rheumatic infection but whose hearts were normal roentgenologically were classified as having "potential

*From the Lymanhurst Health Center, Department of Cardiac Activities, Minneapolis, Minn.

Read before the Meeting of The American Heart Association in San Francisco, June 10, 1938.

Received for publication Aug. 20, 1938.

heart disease" whether they had a systolic murmur or not, and were not included in this study.

Those who had loud, harsh murmurs at the base of the heart considered characteristic of congenital heart disease were excluded even though the heart was found to be normal in size and contour.

Although this group is small, it consists of patients who were carefully selected and in whom a diagnosis of nonpathologic murmur was based on a careful history and physical examination, including roentgenologic studies, electrocardiograms, and other necessary laboratory procedures. These patients had been referred to the clinic for cardiac examination because a murmur had been found in the heart either by the school physician or family doctor. In many of them a previous diagnosis of leakage of the heart had been made, and a number of them had been refused life insurance or had been "rated up" because of a heart murmur.

TABLE I
AGE OF PATIENTS

YEARS OF AGE	FIRST EXAMINATION		TOTAL	LAST EXAMINATION		TOTAL
	MALE	FEMALE		MALE	FEMALE	
5-10	39 (65.0)	23 (35.9)	62 (60.8)	9 (40.9)	12 (54.5)	21 (20.6)
11-15	21 (50.0)	19 (45.2)	40 (39.2)	23 (69.7)	10 (29.4)	33 (32.4)
16-20				24 (53.3)	19 (44.2)	43 (42.2)
21-25				4 (80.0)	1 (20.0)	5 (4.9)
Total	60 (58.8)	42 (41.2)	102	60 (58.8)	42 (41.2)	102

Age of Patients.—Table I indicates that a total of 102 patients were studied, of whom sixty were males and forty-two females. The ages of these patients at the first and last examinations are given. The common belief that functional murmurs are more common in the female is not borne out by these figures. About one-half of the patients were followed from childhood to early adult life.

TABLE II
YEARS FOLLOWED WITH RELATION TO CHANGE IN DIAGNOSIS
(Average Number of Years Followed 4.6)

YEARS FOLLOWED	NUMBER OF CASES	NO CHANGE	NO HEART DISEASE	CONGENITAL HEART DISEASE	RHEUMATIC HEART DISEASE	POSSIBLE EARLY HYPERTENSION
2-4	61 (59.8)	47 (77.0)	11 (18.0)	2 (3.3)	1 (1.6)	
5-8	31 (30.4)	24 (77.4)	4 (12.9)			3 (9.7)
9-12	10 (9.8)	5 (50.0)	2 (20.0)	1 (10.0)		2 (20.0)
Total	102	76 (74.7)	17 (16.7)	3 (2.9)	1 (1.0)	5 (4.9)

Number of Years Followed and Change of Diagnosis.—Table II correlates the number of patients in whom a change of diagnosis was made with the number of years observed. In seventy-six children the murmur persisted throughout, in seventeen the murmur disappeared, while in three instances the diagnosis was changed to "probable congenital

heart disease." This change in diagnosis was based both on an alteration in the intensity of the murmur and roentgenologic changes. It is of interest to consider somewhat in detail these three patients. The first patient was initially examined in 1928, when he was 8 years of age. At that time a localized systolic murmur was found at the apex. The roentgenologic examination revealed that the heart was normal in size and contour. The patient was not examined again until 1932, when the same murmur was again heard, but on roentgenologic examination the heart was found to be moderately enlarged. The contour was considered atypical. The electrocardiogram was normal but a definite diagnosis could not be made. The patient was examined each year thereafter until February, 1938. It was not until 1938 that a definite diagnosis of congenital heart disease was made. The second patient was first examined in 1935, when a short harsh murmur was heard along the left border of the sternum. The murmur was thought to vary considerably with respiration and was not transmitted. A diagnosis of nonpathologic murmur was made. The patient was not seen again until February, 1938, when, as a result of clinical and roentgenologic examinations, a fairly definite diagnosis of congenital heart disease was made. In this case, the roentgenologic examination revealed that the heart was normal in size. There was, however, a moderate enlargement of the pulmonary artery, especially well demonstrated on fluoroscopic examination, which was thought to be quite characteristic of congenital heart disease. In the third case, the patient was first examined in 1935, when a systolic murmur was heard over the base of the heart. The murmur was then thought to be of no importance. He was again examined in 1936. The same murmur was heard and it was still considered nonpathologic in nature. Roentgenologic examination revealed that the heart was normal in size and contour on both occasions. However, in April, 1938, when the patient was re-examined, the murmur had become much louder and much more prolonged and was heard along the left border of the sternum as well as at the apex. The teleoroentgenogram and esophagram revealed that the heart was normal in size and contour. However, on fluoroscopy, there was slight enlargement of the pulmonary artery, and this finding, together with the increased length and intensity of the murmur, was considered at least suggestive of congenital heart disease.

Twenty-nine of these patients when originally examined gave a history of so-called "growing pains" which we considered nonrheumatic in nature. Many such patients are being considered rheumatic because of "growing pains" alone, and no attempt is made to differentiate such patients from those suffering from subacute rheumatic fever. It has been my contention³ that such a differentiation is possible by careful clinical analysis. The results of this follow-up study tend to substantiate my point of view, as none of these twenty-nine patients subsequently

developed rheumatic heart disease. The one patient who developed aortic regurgitation gave no history of rheumatic fever or of "growing pains." He was examined first in 1935, when a localized systolic murmur was heard at the apex. This was considered functional in nature. On repeated examinations, from 1935 to 1937, the same murmur was heard, while roentgenologic studies revealed that the heart was normal in size and contour. In 1938, however, a faint diastolic murmur was heard along the left border of the sternum and the heart was slightly enlarged; the contour suggested early left ventricular enlargement.

In five patients the diagnosis was changed to "possible early hypertension." The systolic blood pressure was between 140 and 150 mm. Hg in four of them; while in one case the blood pressure was 180/94. These patients were all males, and their ages ranged from 17 to 26 at the final examination. At first glance this might appear to be of significance, but it has been observed⁴ that of any group of young people followed over a period of years 4 to 5 per cent will show mild hypertension by the time they reach early adult life.

Of the 102 cases in which nonpathologic murmur was originally diagnosed, in one instance a definite diagnosis of congenital heart disease was finally made, while in two instances it was concluded that a congenital lesion was possibly present. In one case aortic regurgitation developed; while in five instances early hypertension seemingly occurred. If these last five subjects are considered normal and the two questionable congenital lesions are excluded, it can be concluded that a correct diagnosis of nonpathologic murmur was made in 98 per cent of our cases.

Location and Intensity of Murmurs.—It has been pointed out by a number of investigators that the murmurs of greater intensity and length are much more likely to be significant of organic heart disease. Levine,¹ in his recent report, states that murmurs which were found to be functional in nature were usually short and of slight intensity. It is of interest, then, to classify the murmurs in the patients observed in this study. We have used an arbitrary classification of one plus to five plus, similar to Levine's classification; a one-plus murmur indicates a systolic murmur heard well into systole, but short and not intense. These were definite murmurs and not simply roughening of the first sound. The two-plus murmur is somewhat louder and longer, etc., until, by a five-plus murmur, is meant one which is very loud and very rasping, such as is heard most commonly in congenital heart disease.

Fig. 1 reveals that our findings tend to corroborate the point of view that the great majority of murmurs found to be nonpathologic in nature are of slight intensity.

Change in Diagnosis with Relation to Intensity and Transmission of Murmurs.—It seemed of value to determine whether or not the intensity and transmission of murmurs were significant in relation to the change in

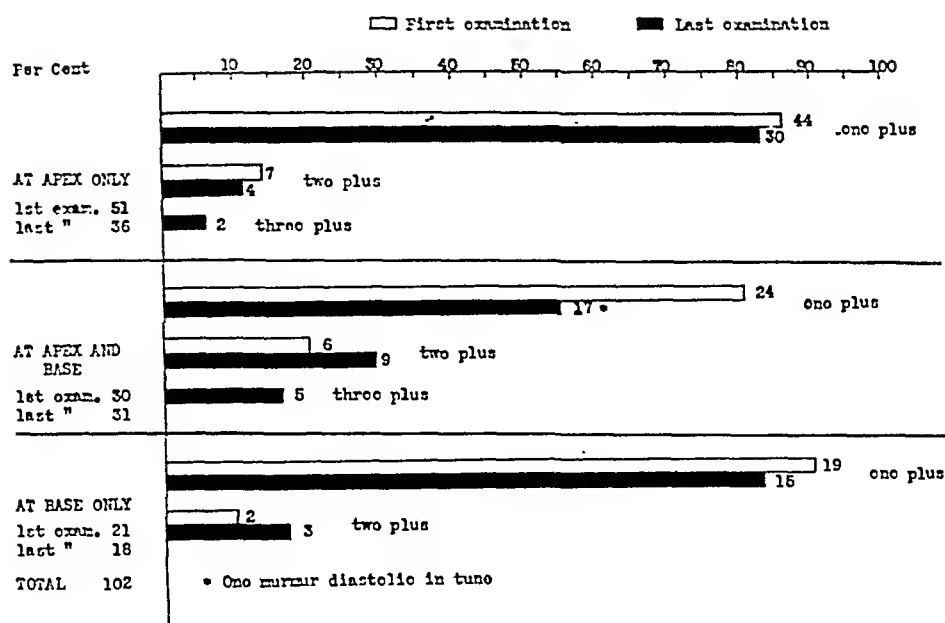


Fig. 1.—Location and intensity of murmur. Intensity of murmurs rated one-plus to five-plus.

diagnosis. It has long been taught that murmurs of greater intensity which were well transmitted into the axilla or heard through to the back and those which obscured the first sound were most probably due to organic heart disease. It is to be noted (Fig. 2) that in almost every

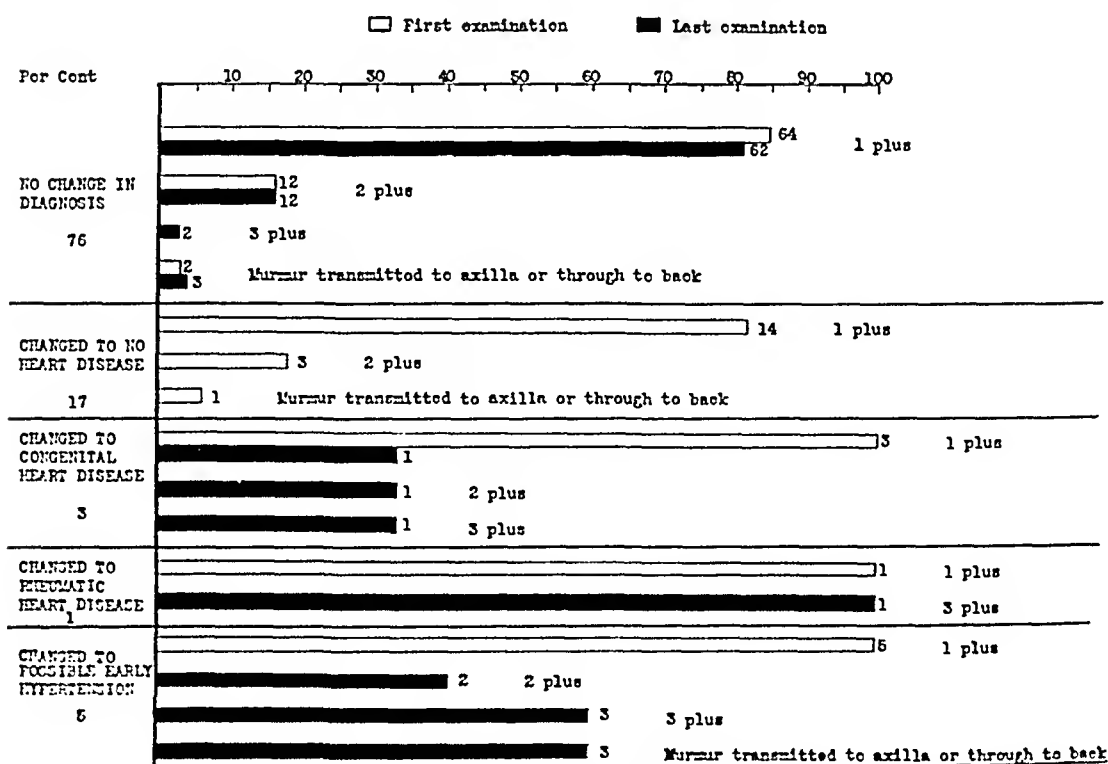


Fig. 2.—Change in diagnosis in relation to intensity and transmission of murmur. Intensity of murmurs rated one-plus to five-plus.

instance in which the diagnosis was changed to organic heart disease or possible early hypertension, the murmur became greater in intensity and was heard in the axilla or through to the back. These findings would tend to indicate that murmurs of greater intensity are more suggestive of organic heart disease and that most functional systolic murmurs are short, do not obscure the first sound, and are rarely heard in the axilla or through to the back.

Roentgenologic Studies.—Probably one of the most important methods of differentiating between murmurs of organic nature and those considered functional is the roentgenologic examination, including fluoroscopy. For a number of years in our clinic it has been customary to obtain at least a teleroentgenogram of every patient who reported, whether or not clinical evidence of heart disease was noted. We have been able to keep down the expense of this procedure by the use of paper films. These films have proved entirely satisfactory as far as our work is concerned.

At the first examination all but one of these patients had a teleroentgenogram. Twenty-two of them had lateral films, with the esophagus filled with barium, as well. The hearts of all of them were considered normal in size and contour. At subsequent, and especially at the last examination, every patient had posteroanterior and lateral films taken and forty-two were fluoroscoped.

The importance of fluoroscopy as well as oblique films of the heart has been stressed in recent years.⁵ There can be no question that free use of the roentgenologic method will aid greatly in cardiac diagnosis. In children and young adults, however, considerable experience is necessary in interpreting oblique films. This is especially true of fluoroscopy. As is well known, the heart in the young appears relatively large and, in many instances, it is difficult to decide definitely whether or not a slight enlargement of the conus pulmonus or pulmonary artery is present. It is my impression that roentgenologic studies of the heart are more efficiently done and prove of more practical value when carried out by the cardiologist rather than the roentgenologist. It is significant, too, that, in sixteen of the 102 patients, at the first roentgenologic examination mention was made of "possible slight cardiac enlargement" or "possible slight enlargement of the conus pulmonus or pulmonary artery," and yet follow-up study showed that the heart was normal in every one of these patients. The cardiothoracic ratio so commonly used at present in measuring the heart is notoriously incorrect. This is especially true in growing children. In children with normal hearts, at one age the transverse diameter of the heart may be slightly over 50 per cent of the total transverse diameter of the chest, and yet on subsequent examinations, with no disease developing in the heart, the size of the heart will be found normal.

The electrocardiogram was found to be of little value in differentiating between functional and organic murmurs. At the first examination, eighteen were obtained, while at the last examination fifty-seven were taken, and in none of them were abnormalities found.

There have been a number of recent studies indicating that the functional systolic murmur is commonly produced by increased velocity of blood flow. It is well known that with tachycardia murmurs often appear at the apex and base of the heart and commonly disappear when the heart slows down. In our group of cases, however, only in nine patients was a rapid heart rate noted. It has also been stated that underweight individuals whose chests tend to be flat are those who most commonly present nonpathologic murmurs. In the great majority of our patients the height and weight were within normal limits.

DISCUSSION

This study indicates that every systolic murmur is of importance and needs to be carefully considered before concluding that it is nonpathologic. It also corroborates the point of view that short murmurs of slight intensity, whether they occur at the apex or base of the heart, are most probably nonpathologic, especially when they are not well transmitted. Follow-up examinations show, however, that with careful history taking and complete physical examinations, including roentgenologic studies, a diagnosis of nonpathologic murmur can be made with a high degree of accuracy.

CONCLUSIONS

(1) One hundred two patients with nonpathologic systolic murmurs were followed over a period of years, and the original diagnosis was found to be correct in 98 per cent.

(2) Murmurs of nonpathologic nature are most likely to be short and of slight intensity and are not well transmitted.

(3) A diagnosis of nonpathologic murmur can be made with a high degree of accuracy if careful histories are taken and complete physical examinations, including, especially, roentgenologic studies, are made.

REFERENCES

1. Levine, S. A.: The Systolic Murmur: Its Clinical Significance, *J. A. M. A.* 101: 436, 1937.
2. White, P. D.: The Clinical Significance of Apical Heart Murmurs, *Am. J. M. Sc.* 174: 731, 1927.
3. Shapiro, M. J.: The Natural History of Childhood Rheumatism in Minnesota, *J. Lab. and Clin. Med.* 21: 564, 1936.
4. Personal Communication with Dr. Harold Diehl, Dean of the Medical School, University of Minnesota.
5. Kurtz, C. M.: *Orthodiascopy*, New York, 1937, The Macmillan Company.

TRANSIENT BUNDLE BRANCH BLOCK AND OTHER
ELECTROCARDIOGRAPHIC CHANGES IN
PULMONARY EMBOLISM*

THOMAS M. DURANT, M.D., I. W. GINSBURG, M.D., AND
HUGO ROESLER, M.D.
PHILADELPHIA, PA.

REPORTS of studies concerning the electrocardiographic changes in cases of pulmonary embolism have been appearing in the medical literature with increasing frequency. The purpose actuating these studies has been the search for characteristic changes which might aid in the differentiation of this condition from coronary occlusion, a differentiation which has often been the source of great difficulty to the practitioner. The clinical features so often relied upon for the diagnosis of coronary occlusion may be duplicated in practically every respect by pulmonary embolism. This is true of the sudden onset with collapse, dyspnea, and vomiting, the substernal pain, the drop in blood pressure, and the fever and leucocytosis. Furthermore, a pericardial friction rub may be heard in pulmonary embolism, due presumably to dilatation of the pulmonary artery and conus, thus leading to confusion with the friction rub so often heard in anterior cardiac infarction. The hemoptysis and pleural friction rub classically associated with pulmonary embolism are frequently absent in that condition.

Differentiation of the two conditions by means of the electrocardiogram has not yet been established on a solid foundation. McGinn and White,¹ in discussing "the acute cor pulmonale" of pulmonary embolism, demonstrated electrocardiographic changes of a temporary nature, consisting in the presence of a Q-wave and late inversion of the T-wave in Lead III, a rather low origin of the T-wave with a gradual, staircase ascent of the ST interval in Lead II, a prominent S-wave and a slightly low origin of the T-wave in Lead I, and an upright T-wave (with inverted P- and QRS-waves) in Lead IV. Such changes in the standard electrocardiogram simulate those seen in infarction of the diaphragmatic surface of the heart (the so-called Q_3T_3 type of electrocardiogram). These authors believed that Lead IV would serve for differentiation inasmuch as this lead may show an abnormal T-wave, whereas in infarction of the diaphragmatic surface of the heart T_4 is usually normal. Barnes² was in accord with McGinn and White concerning the importance of Lead IV, and emphasized the diagnostic importance of the large S_1 in pulmonary embolism, a deflection usually absent, or very small, in the T_3 type of electrocardiogram of coronary thrombosis.

*From the Department of Internal Medicine, Temple University Medical School.
Received for publication Aug. 27, 1938.

Love and Brugler,² however, in a recently reported study of five cases of pulmonary embolism, pointed out that S_1 was present in only two of their cases, and that T_4 was often of no value in the differentiation from coronary thrombosis. In two of their cases, marked S-T segment depression was present in Lead I. They have concluded that there is no electrocardiogram characteristic of pulmonary infarction.

The purpose of this communication is to report three cases of pulmonary embolism, observed at Temple University Hospital, in which striking serial electrocardiographic changes were observed. A study of these electrocardiographic changes reveals further information which may be of value in clarifying the sequence of electrocardiographic events associated with acute pulmonary disorders, and make possible a more accurate means of differentiation from coronary occlusion.

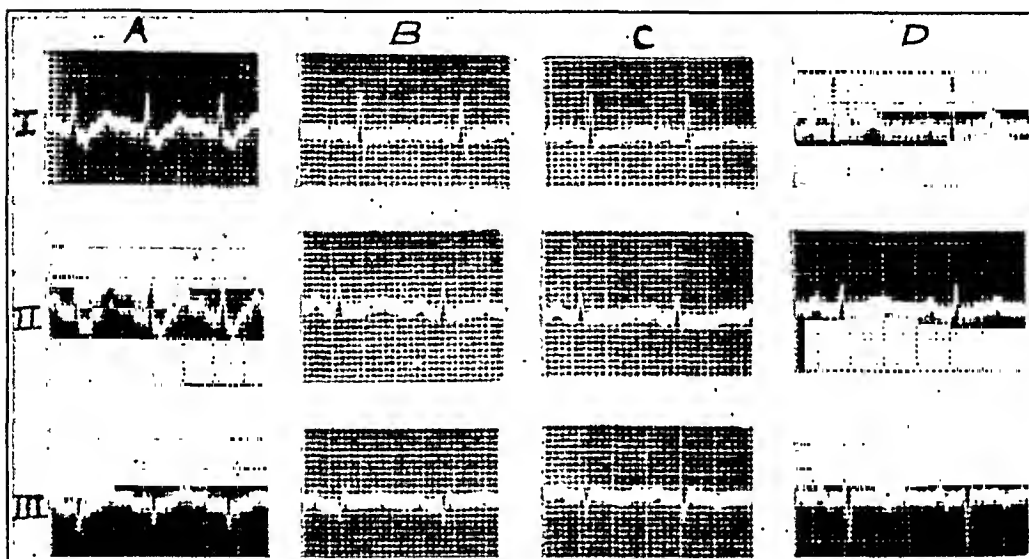


Fig. 1.—Serial electrocardiograms in Case 1. A, Two hours after onset of symptoms of pulmonary embolism; B, twelve hours after onset; C, forty-eight hours after onset; D, twenty days after onset. For description, see text.

CASE 1.—J. M., a man 69 years old, was admitted to Temple University Hospital Feb. 7, 1936, for treatment of an intracapsular fracture of the left femur which had been incurred three days previously. History and examination were entirely negative except for the findings relative to the fracture. On Feb. 11, 1936, a Smith-Peterson nail was introduced, under spinal anesthesia, to secure fixation of the fragments. The patient's postoperative condition was good. On Mar. 3, 1936, while sitting in bed, he suddenly experienced severe dyspnea, became markedly cyanotic, and perspired profusely. There was no pain. The blood pressure was 68/40. Stimulants were administered and the patient placed in an oxygen tent. His general condition improved rapidly, and the following day the blood pressure was 116/70. Electrocardiograms were taken at intervals of two hours, twelve hours, forty-eight hours, and twenty days after the attack. These are shown in Fig. 1. A roentgenogram of the chest taken three days after the attack showed an area of abnormal density in the right lung field.

CASE 2.—D. P., a woman 56 years of age, was admitted to Temple University Hospital July 24, 1934, complaining of severe pain in the right upper quadrant of the abdomen. She had had an attack of gall bladder colic two years previously, but the

history was otherwise negative. Operation on the day of admission showed acute pancreatitis and cholangitis. A cholecystostomy was done, and the abdomen drained. The postoperative course was stormy. On the twenty-second postoperative day she experienced sudden, severe, precordial pain and oppression, dyspnea, and anxiety. There were marked cyanosis, circumoral pallor, a rapid, thready pulse, and profuse perspiration. The blood pressure was 84/60. Recovery from this attack was

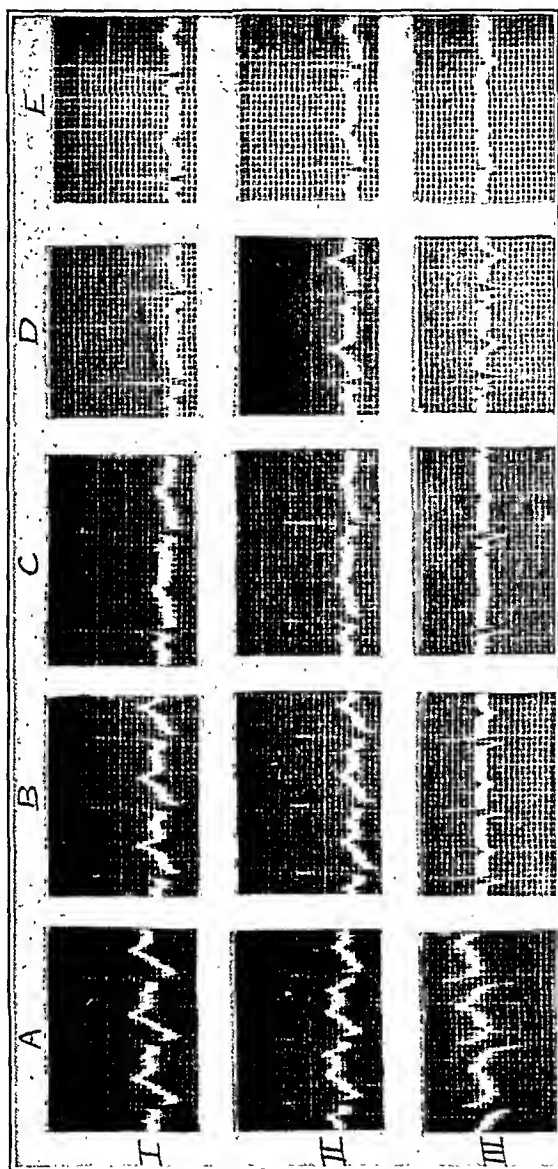


Fig. 2.—Serial electrocardiograms in Case 2. A, Taken within two hours after onset of symptoms of pulmonary embolism; B, five hours after onset; C, twenty-two hours after onset; D, five days after onset; E, three years later. For description, see text.

very slow, and was later complicated by the development of a left-sided perinephritic abscess which was drained on Sept. 11, 1934. Eventually the patient made a complete recovery, and on a recent visit to the hospital (Nov. 15, 1937) a complete examination, including thorough cardiac study, was entirely negative, except for the possibility of residual gall bladder disease. Electrocardiograms taken at intervals following the attack of pulmonary embolism and again at the time of the recent examination are reproduced in Fig. 2. The diagnosis of pulmonary infarction was substantiated in this case by the roentgenologic findings soon after the attack.

CASE 3.—M. B., a woman 54 years of age, was admitted to Temple University Hospital April 28, 1938, complaining of pain in the left loin and hematuria. Examination was negative except for obesity and a blood pressure reading of 170/90. A left-sided pyelolithotomy was performed on April 30, 1938. There were no unusual postoperative developments until the twelfth postoperative day, when the patient suddenly felt weak and cold, and noted tightness under the sternum. She was markedly dyspneic, cyanotic, and apprehensive. There was profuse perspiration. The pulse was regular and its rate was 120 a minute. Crepitant râles were heard at the base of the right lung. The blood pressure was 132/84. The patient's condition gradually improved, and by May 5, 1938, the blood pressure had risen to the preoperative level. Pleural pain over the base of the right lung developed on May 14, 1938, and persisted until May 25, 1938. The râles were continuously present throughout this period, together with dullness and diminished breath and voice sounds over the right lower lobe. The patient made an uneventful recovery following this and was discharged on June 2, 1938, in good condition.

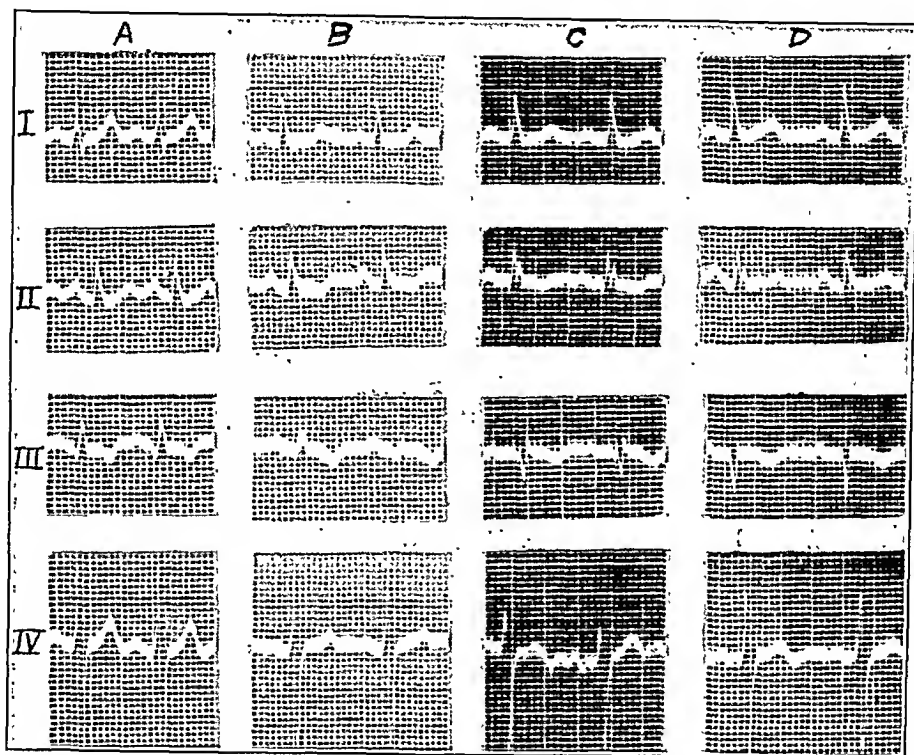


Fig. 3.—Serial electrocardiograms in Case 3. A, Taken six hours after onset of symptoms of pulmonary embolism; B, twenty-four hours after onset; C, six days after onset; D, twenty days after onset. In Lead IV relative negativity of the anterior electrode is represented by a downward deflection. For description, see text.

The first electrocardiogram was not taken in this case until six hours after the onset of symptoms of embolism. This electrocardiogram, together with subsequent tracings, is reproduced in Fig. 3. The patient was given 1.3 gm. of digitalis in the interval between curves A and B. No digitalis was given following this.

DISCUSSION OF ELECTROCARDIOGRAMS

For purposes of convenience and clarity in description, the discussion of the electrocardiographic changes in the cases above reported will be divided into the early and later changes. The early changes are those which appear within an hour or two after onset; while the later changes,

which consist in a gradual reversion of the early changes toward the normal, are seen some hours later, and extend over a period of days. It will be apparent from the discussion that the serial changes are much more rapid in their progression than are those following coronary occlusion.

Early Changes.—The early electrocardiograms in Cases 1 and 2 (Figs. 1A and 2A, respectively) were taken within two hours of the onset of pulmonary embolism. Intraventricular block is present in each, and is of the type shown by Wilson, et al.,⁴ to be due to a conduction disturbance in the right bundle branch. In Case 1 the QRS interval measures 0.13 second, and in Case 2 it measures 0.12 second. In both instances there is an initial, narrow, upward spike, followed by a broad, U-shaped S-wave in Leads I and II. In Lead III in Case 2 there is a broad R-wave corresponding to the S-wave in the other two leads.

The majority of electrocardiograms published in the literature as examples of the changes occurring in pulmonary embolism are curves taken at longer intervals following the onset of symptoms than are these first curves. One curve obtained by McGinn and White, however, was taken two hours after the attack. This electrocardiogram showed a rather broad, somewhat rounded S-wave in Lead I, similar in contour to that seen in our cases, but without prolongation of the QRS interval beyond normal limits. This curve would seem to represent a stage of transition between our early changes and those to be described as later changes.

In two of the five cases reported by Love and Brugler there may have been early changes, but the exact time at which the electrocardiograms were taken is not mentioned in their report. The electrocardiograms in these two cases do not show QRS prolongation, but, instead, marked displacement of the S-T segment in all leads.

Pick⁵ has published an electrocardiogram taken before, and another taken a few minutes after, the onset of pulmonary embolism. The electrocardiogram before the attack showed a QRS interval of 0.08 second, and was normal except for slight left axis deviation, but the curve taken immediately after the attack showed right bundle branch block with broad S-waves in Leads I and II and a QRS interval of 0.12 second. The patient died four hours after the onset of symptoms. Post-mortem examination showed an embolus involving the main stem of the pulmonary artery. No coronary or myocardial disease was found.

In another case seen by one of us (T. M. D.) at the Desert Sanatorium of Southern Arizona, but not reported in detail in this article, right bundle branch block was observed in the electrocardiogram of a patient with pulmonary tuberculosis who had developed thrombotic occlusion of the artery to the middle lobe of the right lung with ensuing infarction and abscess formation in that lobe. The clinical picture with the onset of the infarction was similar to that of coronary occlusion, and included

the presence of a pericardial friction rub on the day of onset of symptoms. The electrocardiogram, taken within two hours of the onset of the attack, showed a broad S-wave in Lead I, and a QRS interval of 0.1 second. At post-mortem examination no evidence of coronary or myocardial disease was found.

Later Changes.—The transient character of the bundle branch conduction disturbance in cases of pulmonary embolism in which the patient recovers is demonstrated by its total absence in curves taken five hours (Case 2, Fig. 2B), and twelve hours (Case 1, Fig. 1B) after onset. The QRS complex is of normal duration in both, and the broad U-shaped S-wave in Lead I has been supplanted by a sharp, narrow deflection. The staircase ascent of the S-T segment is now well demonstrated in Case 2. This latter phenomenon is also of short duration, however, having given way to a more normal contour in the curve taken twenty-two hours after onset (Fig. 2C). In Case 1 the staircase ascent of the S-T segment was not present in the second curve, but this may be due to the fact that it was taken at a longer interval after onset (twelve hours) than was the second curve in Case 2, or the first curves of McGinn and White.

An important feature in the later serial changes is the eventual disappearance of the S-wave in Lead I. In Case 1 it had disappeared in the curve taken twenty days after the attack. In Case 2 it was still present in the curve taken five days after onset, but had disappeared in the curve taken three years later. It is possible, of course, that the disappearance in this case may have taken place at a time corresponding to that in Case 1, but interval electrocardiograms are lacking to demonstrate this point. In Case 3 the S-wave in Lead I had disappeared in the curve taken twenty-four hours after the attack (Fig. 3B).

The series of electrocardiograms in Case 3 (Fig. 3) lacks a curve taken within six hours after the onset of pulmonary infarction, when the intraventricular conduction disturbance in Cases 1 and 2 was demonstrated. The first curve in this series corresponds in contour with Fig. 2B of Case 2, and was taken at a similar interval after onset of symptoms. It presents an S-wave in Lead I, a staircase ascent of the S-T segment in Lead I, and, in Lead III, a Q-wave with an inverted T-wave. In the second electrocardiogram, taken twenty-four hours after onset, and in the subsequent curves, the S-wave in Lead I is absent. The S-T changes in Leads I and II have been modified, probably by reason of the digitalis received by the patient in the interval between the taking of the first and second curves.

Lead IV was not taken with sufficient frequency in this series of cases to allow any conclusions to be drawn concerning its characteristics. In Case 3, the only one in which this lead was used throughout, the first curve showed a positive, or normal, T₄. This was modified somewhat in the later curves, possibly by the effect of digitalis. In this case

Lead IV would have been of no value in differentiating between pulmonary embolism and coronary occlusion. Unfortunately this lead was not taken in either Case 1 or Case 2 at a time when the intraventricular conduction disturbance was present.

COMMENT

A review of the standard leads in the three cases reported, together with a study of curves published by others, leads us to the opinion that there is a rapid series of electrocardiographic changes associated with acute pulmonary heart disease which may be summarized as follows:

Early.—(1) Intraventricular block of the right bundle branch type, with a broad, shallow S-wave in Lead I and II; (2) marked depression of the S-T segment in Leads I and II may be present, as in the cases reported by Love and Brugler.

Later.—(1) Re-establishment of normal intraventricular conduction associated with the supplanting of the broad S-wave in Leads I and II by a wave of sharp, narrow contour; (2) a sloping ascent of the S-T segment in Leads I and II; (3) a Q-wave and inverted T-wave in Lead III.

Subsequently.—A disappearance of the above changes by a gradual process of reversion toward the normal, except for the persistence, in some, of the changes in Lead III.

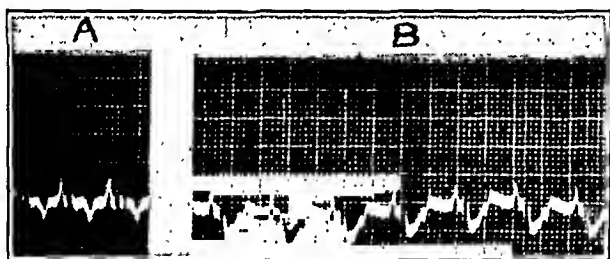


Fig. 4.—Electrocardiogram (Lead II) of a dog before (A) and after (B) the rapid injection of 30 c.c. of air into the femoral vein.

This series of changes, with its dramatic onset in temporary right bundle branch block and the subsequent reversion to normal, we have never seen in coronary occlusion, nor have we seen it in any condition other than acute pulmonary heart disease. It is true that atypical right bundle branch block of the type described may appear following the onset of coronary occlusion, but, when such is the case, the conduction disturbance does not rapidly subside with a gradual narrowing and eventual complete disappearance of the S-wave in Lead I. We feel that the serial changes described are characteristic of acute pulmonary heart disease, and may prove to be an important diagnostic aid. It is to be emphasized, however, that the most significant features appear very soon after the onset of the condition and disappear very rapidly. In order

to be of the greatest diagnostic value, therefore, the electrocardiographic study should be begun within the first hour or two after the onset of symptoms in a case of suspected pulmonary embolism.

The mechanism responsible for these electrocardiographic changes is not understood. Experimental studies⁶ show that changes in the QRS complex identical with those seen in Fig. 1A and Fig. 2A may be produced in dogs by air embolism from the systemic venous circulation (Fig. 4). These changes come on at a time when there is noted, in open chest experiments, a sudden dilatation of the right ventricle following the injection of the air. Evidence will be published to show that, in these experiments, anoxemia was not responsible for the changes induced by the air embolism. Whether sudden dilatation of the right ventricle can be held as the only factor in their production will require further experimental study.

SUMMARY

Transitory electrocardiographic changes which have their onset in right bundle branch block and occur in association with pulmonary embolism are described and their diagnostic significance discussed. The importance of the very early conduction disturbance, occurring within a few hours of the onset of the condition, and the rapidity with which this disturbance regresses are emphasized.

REFERENCES

1. McGinn, S., and White, P. D.: Acute Cor Pulmonale Resulting From Pulmonary Embolism; Its Clinical Recognition, *J. A. M. A.* 114: 1473, 1935.
2. Barnes, A. R.: Diagnostic Electrocardiographic Changes Observed Following Acute Pulmonary Embolism, *Proc. Staff Meet. Mayo Clinic* 11: 11, 1936.
3. Love, W. S., Jr., and Brugler, G. W.: Electrocardiograms Similar to Those of Coronary Thrombosis With Especial Reference to Those Obtained in Pulmonary Infarction, *Southern M. J.* 30: 371, 1937.
4. Wilson, F. N., Johnston, F. D., Hill, I. G. W., Macleod, A. G., and Barker, P. S.: The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S-Deflections in Lead I, *AM. HEART J.* 9: 459, 1934.
5. Pick, A.: Beitrag zur Frage des atypischen Schenkelblockes, *Ztschr. f. klin. Med.* 129: 719, 1936.
6. Durant, T. M., and Ginsburg, I. W.: Electrocardiographic Changes in Experimental Air Embolism, To be published.

TUMORS OF THE HEART AND PERICARDIUM*†

ROY W. SCOTT, M.D., AND CURTIS F. GARVIN, M.D.

CLEVELAND, OHIO

MANY references to tumors of the heart and pericardium are found in past writings, but most of these are concerned with isolated case reports. The prevailing impression is that tumors of the heart and pericardium are quite rare. In 298 autopsies on patients with malignant disease, Symmers¹ found discrete metastases in the heart in only five cases (1.6 per cent). Statistical studies of Kitain,² Janusz,³ and others record only occasional cases in which there were myocardial metastases. In a recent review of the subject, Yater⁴ lists numerous autopsy series that have been investigated in regard to the occurrence of cardiac metastases and concludes that tumors of the heart and pericardium are rare.

Since Yater's review, five additional series have been published. Lymburner⁵ found fifty-two secondary and four primary tumors of the heart in 8,500 autopsies at the Mayo Clinic. Pollia and Gogol⁶ studied 12,000 autopsies at the Los Angeles General Hospital and found 1,450 cases of malignant tumors with twenty-nine secondary tumors of the heart. Helwig⁷ reported nine cases of tumor of the heart in 1,000 autopsies at St. Luke's Hospital in Kansas City. Burke⁸ reported fourteen metastatic tumors of the heart in 327 cases of known malignant disease. Willis,⁹ in 323 autopsies on patients with malignant tumors of all kinds, found metastatic growths in the myocardium in twenty cases, an incidence of 6.2 per cent.

Among 1,082 cases of malignant disease appearing in a series of 11,100 consecutive post-mortem examinations performed at the Cleveland City Hospital during the past twenty years, the heart was involved by metastases in 79; the parietal pericardium in 61; the heart and parietal pericardium together in 22; and the heart or parietal pericardium, or both, in 118. These results are summarized in Table I.

In this study, sarcoma and lymphoblastoma* involved the heart and pericardium relatively more often than did carcinoma, but the number of cases of sarcoma and lymphoblastoma in the series is small, so that no definite conclusion can be made. Actually carcinoma accounted for most of the cases, as shown in Table II.

*From the Department of Medicine of Cleveland City Hospital and the School of Medicine of Western Reserve University.

†Read in abstract at the Meeting of the American Heart Association held at San Francisco, Calif., on June 10, 1938.

Received for publication Aug. 29, 1938.

*Under lymphoblastoma are included cases of lymphatic leucemia, lymphosarcoma, Hodgkin's Disease, and reticulum cell sarcoma.

TABLE I

INCIDENCE OF INVOLVEMENT OF THE HEART AND PERICARDIUM IN 1,082 CASES OF MALIGNANT DISEASE

	NUMBER OF CASES	PERCENTAGE OF 1,082 CASES OF MALIGNANT DISEASE
Heart	79	7.3
Parietal pericardium	61	5.7
Both heart and parietal pericardium	22	2.0
Heart or parietal pericardium or both	118	10.9

TABLE II

INCIDENCE OF INVOLVEMENT OF THE HEART AND PERICARDIUM BY CARCINOMA, SARCOMA, LYMPHOBLASTOMA, MYELOGENOUS LEUCEMIA, AND MIXED TUMORS

TUMOR TYPES	NO. OF CASES	METASTASES TO HEART	METASTASES TO PARIETAL PERICARDIUM	METASTASES TO HEART OR PARIETAL PERI- CARDIUM OR BOTH
Carcinoma	943	53	54	89
Sarcoma	61	11	5	13
Lymphoblastoma	57	13	1	14
Myelogenous leucemia	14	2	1	2
Mixed tumors	7	0	0	0
	1082	79	61	118

In the cases recorded in the literature, metastases to the heart and pericardium have occurred from neoplasms involving practically every organ of the body. The distribution of the primary tumors metastasizing to the heart and pericardium in our material is shown in Table III.

From Table III it is apparent that carcinoma of the bronchus and breast is of paramount importance as a source of secondary tumors of the heart and pericardium, the incidence of involvement being 35.6 per cent in both instances. Reticulum cell sarcoma, melanoma, lymphatic leucemia, and chloroma metastasized to the heart frequently (all 50 per cent or more), but the number of cases is too small to be of statistical significance.

Our observations show that true embolic metastasis via the coronary arteries was the most common mode of involvement of the heart. Direct extension from either a primary or secondary tumor in the lung or a secondary tumor in the mediastinal lymph nodes was next in frequency, and invasion through the lymphatics (retrograde in the case of the heart, Aubertin,¹⁰ Wolf and Giet¹¹) was the least common.

The most common mode of involvement of the parietal pericardium was by extension. Hematogenous metastasis was next in frequency, and lymphatic metastasis was least common. Table IV summarizes the findings in regard to the mode of involvement.

TABLE III

THE DISTRIBUTION OF ONE HUNDRED EIGHTEEN SECONDARY TUMORS OF THE
HEART AND PERICARDIUM

PRIMARY TUMOR	NUMBER OF CASES	METASTASES TO HEART	METASTASES TO PARIETAL PERICARDIUM	METASTASES TO BOTH HEART AND PARIETAL PERICARDIUM	METASTASES TO HEART OR PARIETAL PERICARDIUM OR BOTH
Carcinoma of bronchus	115	30	26	15	41
Carcinoma of breast	45	3	13	0	16
Reticulum cell sarcoma	9	6	0	0	6
Melanoma	10	5	2	2	5
Lymphatic leucemia	11	6	0	0	6
Chloroma	3	2	0	0	2
Leiomyosarcoma	6	1	2	0	2
Carcinoma of bladder	25	0	1	0	1
Carcinoma of cervix	49	2	0	0	2
Carcinoma of colon	27	0	1	0	1
Carcinoma of esophagus	61	2	2	0	4
Carcinoma of kidney	19	3	1	1	3
Hypernephroma	12	1	0	0	1
Carcinoma of liver	21	2	1	0	3
Carcinoma of pharynx	9	1	0	0	1
Carcinoma of lip	5	1	0	0	1
Carcinoma of ovary	19	1	0	0	1
Carcinoma of pancreas	45	2	2	0	4
Carcinoma of prostate	56	0	2	0	2
Carcinoma of rectum	39	2	2	1	4
Carcinoma of stomach	201	1	1	0	2
Metastatic carcinoma	16	2	1	1	2
(primary undetermined)					
Neurofibrosarcoma	2	1	0	0	1
Retroperitoneal sarcoma	2	0	1	0	1
Liposarcoma	1	1	0	0	1
Round cell sarcoma	4	1	0	0	1
Lymphosarcoma	13	1	1	1	1
Hodgkin's Disease	22	0	1	0	1
Myelogenous leucemia	14	2	1	1	2
Miscellaneous*	221	0	0	0	0
	1082	79	61	22	118

*Refers to a variety of tumors which in this series did not metastasize to the heart or pericardium.

TABLE IV

THE FREQUENCY OF THE VARIOUS MODES OF INVOLVEMENT OF THE HEART AND
PERICARDIUM BY SECONDARY TUMORS

MODE OF INVOLVEMENT	HEART	PARIETAL PERICARDIUM
Definitely hematogenous	37	8
Definitely extension	18	25
Definitely lymphatic	0	3
Probably hematogenous	5	6
Probably extension	1	2
Probably lymphatic	0	7
Combinations	4	2
Undetermined	14	8
	79	61

More secondary tumors occurred on the left side of the heart than on the right, but the difference was not great. It would seem that the two sides of the heart are almost equally susceptible (Lymburner,⁵ Bodenheimer¹²). The frequency of involvement of the various portions of the heart by metastatic tumors is as follows:

Parietal pericardium	-	-	-	-	-	-	-	-	-	61
Right auricle	-	-	-	-	-	-	-	-	-	29
Right ventricle	-	-	-	-	-	-	-	-	-	31
Left auricle	-	-	-	-	-	-	-	-	-	29
Left ventricle	-	-	-	-	-	-	-	-	-	45
Septum	-	-	-	-	-	-	-	-	-	11
Undetermined*	-	-	-	-	-	-	-	-	-	6

As others have found, the endocardium was least often involved (thirty cases). The epicardium and myocardium were more commonly the site of secondary tumor with no significant difference between the two (epicardium sixty-two cases and myocardium fifty-five).

The gross appearance of the secondary tumor of the heart varied widely. In some cases there were discrete tumor nodules varying from 1 mm. to 2 cm. in diameter. In other cases there was diffuse infiltration. The pericardial tumors likewise varied widely in nature and extent. Histologically, the tumors followed the pattern of the primary neoplasm. In several instances, tumor cells were found in lymphatic channels, in the coronary arteries, and in thrombotic masses within the chambers of the heart.

The pericardium was the seat of an acute pathologic process in 22 per cent of the cases in this series. The condition of the pericardium in 118 cases of secondary tumors of the heart and pericardium was as follows:

Normal	-	-	-	-	-	-	-	-	-	-	89
Simple effusion	-	-	-	-	-	-	-	-	-	-	5
Bloody fluid	-	-	-	-	-	-	-	-	-	-	7
Purulent pericarditis	-	-	-	-	-	-	-	-	-	-	3
Serofibrinous pericarditis	-	-	-	-	-	-	-	-	-	-	11
Obliteration by tumor	-	-	-	-	-	-	-	-	-	-	1
Fibrous obliteration	-	-	-	-	-	-	-	-	-	-	2

However, patients dying of malignant disease without cardiac metastases occasionally show similar pericardial disease. For example, in a control series of 100 malignant tumors that did not involve the heart or pericardium, acute pericardial disease was found in 7 per cent. In both series the amount of pericardial fluid was frequently insufficient to be detected clinically. It appears from our observations that evidence of pericardial disease in a patient with a known malignant process is a valuable diagnostic sign of cardiac metastases, but not a pathognomonic one.

*This group consisted of cases in which the tumor was found microscopically but the location from which the section was taken was not specified.

In accordance with the experience of others, the majority of the patients in this series showed no demonstrable clinical evidence of cardiac disease. Seven patients exhibited myocardial insufficiency. In five cases there were abnormalities of the cardiac mechanism without cardiac failure. A control series of 100 malignant tumors that did not involve the heart or pericardium failed to show any cases of myocardial insufficiency, but did include two cases in which there were abnormalities of the cardiac mechanism. At autopsy the abnormal cardiac mechanism could not be explained. Accordingly, it appears that myocardial insufficiency developing without apparent cause in a patient with a known malignant process is an important clinical finding pointing to cardiac metastases, while abnormalities of the cardiac mechanism are a suggestive sign, but not a pathognomonic one. Such signs of tumor of the heart as heart block, symptoms referable to the location of the tumor other than heart block, and suggestive roentgenologic observations were not observed in our series.

In only one of these seven cases with myocardial insufficiency due to tumor involvement of the heart was the correct diagnosis made ante mortem. This patient showed both cardiac failure and hemorrhagic pericardial fluid. In this instance the ante-mortem diagnosis of carcinoma of the bronchus with metastases to the heart and pericardium was substantiated at autopsy. The entire heart was extensively involved by tumor. Both layers of the pericardium showed much tumor tissue and an organizing fibrinous pericarditis.

In the remaining six cases heart failure was evident. In three of these cases it was known that the patient had a malignant disease, but in no instance was the possibility considered that tumor involvement of the heart could be responsible for the myocardial insufficiency. At post-mortem examination in all these cases there was extensive involvement of the heart by tumor, with no other explanation for the myocardial insufficiency.

As has been stated, five patients with metastases to the heart showed abnormalities of the cardiac mechanism without cardiac failure. Three of these had carcinoma of the bronchus, diagnosed correctly clinically. One showed paroxysmal auricular fibrillation; one, paroxysmal auricular fibrillation and paroxysmal auricular tachycardia; and one, auricular flutter. In none of these cases was the possibility of cardiac metastases considered. At autopsy, in two of these cases there was severe involvement of the atria by tumor and in one the left ventricle was involved.

The fourth patient, who also had carcinoma of the bronchus, had several attacks of paroxysmal auricular fibrillation. The possibility of cardiac metastases was considered, but a definite clinical diagnosis could not be established. At autopsy, the right atrium was involved by tumor. However, the heart showed a rheumatic mitral stenosis, and whether the

paroxysmal fibrillation was due to the tumor involvement or the rheumatic heart disease could not be determined.

The fifth case was one of melanosareoma of the eye with generalized metastases. The diagnosis was proved clinically by means of biopsy. The patient showed attacks of paroxysmal auricular fibrillation and the possibility of metastases to the heart was thought of but could not be established. At autopsy, tumor tissue involved the left atrium, left ventricle, and the pulmonary conus.

An analysis of the electrocardiograms from these cases of secondary tumors shows, in accordance with Siegel and Young¹³ and others, that there is no configuration pathognomonic of tumor of the heart. The electrocardiographic changes depend principally on the situation of the tumor. In this series, auricular fibrillation, auricular premature contractions, and auricular flutter predominated, and at autopsy in these cases with one exception involvement of the atria was found.

SUMMARY

Among 1,082 cases of malignant disease appearing in a series of 11,100 consecutive post-mortem examinations performed at the Cleveland City Hospital during the past twenty years, the heart, including the pericardium, was involved by metastatic tumor in 118 cases, an incidence of 10.9 per cent. Carcinoma of the bronchus and the breast most often invaded the heart and pericardium and accounted for 48 per cent of the cases in this series.

The development of congestive failure without other apparent cause, in a patient with malignant disease, was the most important clinical finding pointing to cardiac metastasis.

REFERENCES

1. Symmers, D.: The Metastasis of Tumors, *Am. J. M. Sc.* 154: 225, 1917.
2. Kitain, H.: Zur Kenntnis der Häufigkeit und der Lokalisation von Krebsmetastasen mit besonderer Berücksichtigung ihres histologischen Baues, *Virchows Arch. f. path. Anat.* 238: 289, 1922.
3. Janusz, W.: Krebsstatistik des Sektionsmaterials des anatomisch-pathologischen Instituts der Universität zu Lwow, *Ztschr. f. Krebsforsch.* 23: 47, 1926.
4. Yater, W. M.: Tumors of the Heart and Pericardium: Pathology, Symptomatology, and Report of Nine Cases, *Arch. Int. Med.* 48: 627, 1931.
5. Lymburner, R. M.: Tumors of the Heart: Histopathological and Clinical Study, *Canad. M. A. J.* 30: 368, 1934.
6. Pollia, J. A., and Gogol, L. J.: Some Notes on Malignancies of the Heart, *Am. J. Cancer* 27: 329, 1936.
7. Helwig, F. C.: Tumors of the Heart, *J. Kansas M. Soc.* 36: 265, 1935.
8. Burke, E. M.: Metastatic Tumors of the Heart, *Am. J. Cancer* 20: 33, 1934.
9. Willis, R. A.: The Spread of Tumors in the Human Body, London, 1934, J. & A. Churchill, Ltd.
10. Aubertin, C.: Sur un Cas de Thrombose Neoplasique du Coeur Droit, *Arch. de Med. Exper.* 17: 197, 1905.
11. Wolf and Giet: Lymphosarcome Mediastinal: Envahissement du Myocarde, *Bull. Soc. Anat.* 92: 340, 1922.
12. Bodenheimer, K.: Beitrag zur Pathologie der krebsartigen Neubildungen am Herzen, Inaugural Dissertation, Bern, 1865, 47 pp.
13. Siegel, M. L., and Young, A. M.: Electrocardiographic Findings in Tumors of the Heart: With Report of a Case, *AM. HEART J.* 8: 682, 1933.

PREMATURE CLOSURE OF THE FORAMEN OVALE

REPORT OF TWO CASES

MIRIAM C. BENNER, M.D.

DENVER, COLO.

IN THE extensive literature on congenital cardiac anomalies there is almost no mention of premature closure of the foramen ovale. Lehman,¹ in 1927, reviewed the subject and found reports of five cases. He added a case report and presented the following classification of the condition: "(1) Infants with marked edema at birth, (2) infants apparently normal at birth but dying with cyanosis within a few days, and (3) atypical cases modified by other major cardiac anomalies." Two cases which fall in the first group were reported by Tait,² in 1875, and Osler,³ in 1880. Both infants were premature and stillborn. Vieussens,⁴ Smith,⁴ and Lehman reported cases which fall into the second group; and Vernon⁴ reported one which was complicated by other anomalies and so belongs in the third group.

The reports by Tait and Osler are almost identical. In each case there was marked hydramnios during the latter part of pregnancy, followed by premature delivery of a stillborn infant. The placentas were large and edematous, and the infants were so large that delivery was difficult. There was severe generalized edema and a marked waxy pallor of the skin. In both infants the foramen ovale was closed by an overlapping membrane which could be pushed aside to allow the passage of a probe. There was also a widely patent ductus arteriosus in both. In Osler's case there was marked enlargement of the right auricle to 6.8 cm. in circumference, and also dilatation of the right ventricle and hypertrophy of its wall to 8 mm. in thickness. The ductus arteriosus was 1.6 cm. in circumference, as compared to an aorta of 1.7 cm. The liver measured 15.5 cm. by 7 cm., and nothing further was noted. Tait's report did not include measurements, but this author attempted to explain the findings on the basis of a cardiac anomaly which caused hindrance to the passage of blood from the right auricle, with subsequent engorgement of all the vessels in front of the auricle throughout the double circulation. He stated that hydramnios resulted from the engorgement of the placenta.²

Recently two cases have been seen at the University of Colorado School of Medicine. One falls definitely into the first group of Lehman's classification, and the other probably belongs in the second group, since the infant lived for eleven hours and developed cyanosis before death. The fact that marked edema was noted in this second case, and was doubtless present at birth, suggests, however, that Lehman's first two groupings are too arbitrary.

From the Child Research Council and the Department of Pathology, University of Colorado School of Medicine.

Received for publication Sept. 1, 1938.

REPORT OF CASES

CASE 1.—Baby F. *History:* The mother was a 19-year-old bipara and was reported to have a negative blood Wassermann reaction. A stillborn fetus weighing 2750 gm. and measuring 44 cm. in length was delivered spontaneously, and at birth was noted to be very edematous. No other history was available and the infant was sent to us for autopsy.

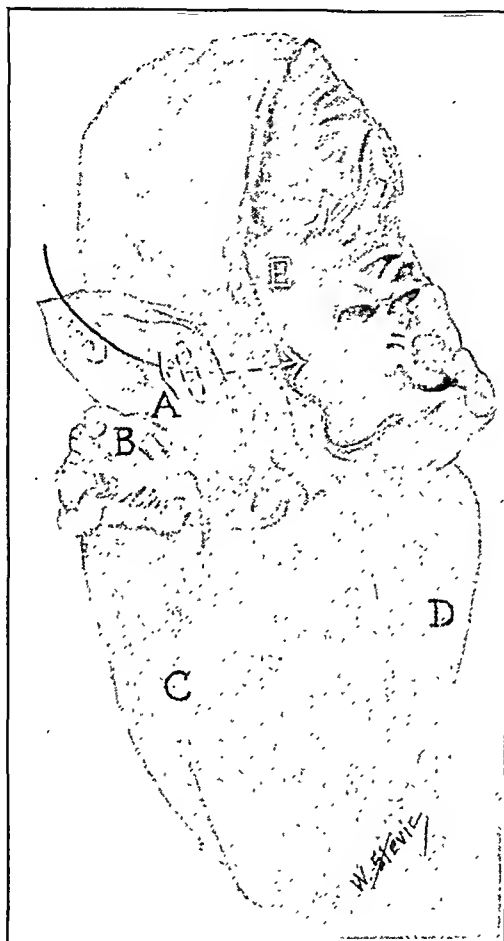


Fig. 1.—Drawing of the heart of Baby F (Case 1), showing foramen ovale with overlapping membrane and hypertrophied right auricle. A, Arrow traversing the foramen ovale; B, left auricle; C, left ventricle; D, right ventricle; E, right auricle (hypertrophied).

Necropsy Report (eight days after death): The body was noted to have a waxy pallor and to be extremely edematous externally, but was otherwise normally formed. On incision of the skin much watery fluid escaped, and all of the body cavities contained considerable sanguineous fluid. The thymus showed extreme involution. The lungs were atelectatic. There was a bilateral otitis media. In this case there was no other focus of infection, which is unusual in a stillborn infant, since the common source of an ear infection is infected amniotic fluid which is likely to penetrate the sinuses and the bronchi as well as the ears.

The heart and the liver showed the most interesting abnormalities. The heart weighed 25 gm. (after fixation). The right auricle was enlarged and was about equal in size to all of the remaining heart tissue; it had a firm, thickened wall. The tricuspid valve appeared slightly thickened but its orifice seemed to be of normal size. The remaining chambers and valves of the heart were normal except that the ductus

arteriosus was widely patent and the foramen ovale was entirely covered by a membrane which overlapped the opening on all sides. From the right auricle a probe approximately 3 mm. in diameter could be pushed into the left auricle by lifting the lower part of the overlapping membrane (Fig. 1). Microscopically the heart showed hypertrophy of the muscle of the right auricle.

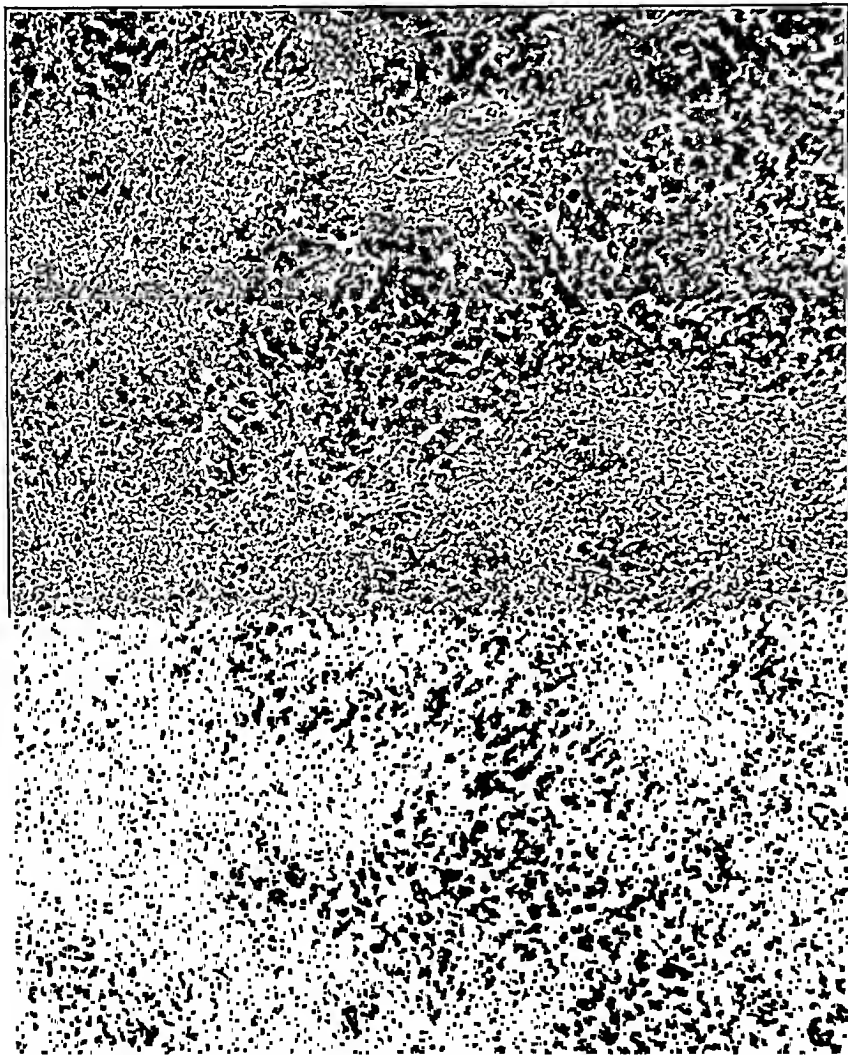


Fig. 2.—Photomicrograph (70 \times) of histologic section of liver, from Baby F (Case 1), showing patchy necrosis around the central veins.

The liver measured 8 by 4.5 by 3 cm. It was firmer than usual and showed some irregularity of the surface. Microscopically there was a slight increase in periportal connective tissue and a striking patchy central necrosis with atrophy of many of the liver cords. The condition was typical of a severe passive congestion (Fig. 2).

The placenta and membranes were not available.

CASE 2.—Baby A. *History:* The mother was a unipara, 19 years of age; the pregnancy was normal; at delivery there appeared to be a moderate hydramnios. The placenta was small and not edematous. The infant was 50 cm. long and weighed 2950 gm. He was difficult to resuscitate and much fluid poured from the nose and

mouth. This fluid had to be removed by repeated suction during all the time the infant lived. The baby never did well, finally became very cyanotic, and died eleven hours after birth.

Necropsy Report (five hours after death): The body was cyanotic and no rigor mortis was present. Generalized edema was present and the subcutaneous tissue was 1.5 cm. in thickness over the thorax and abdomen. Much free fluid escaped on incision of the skin. The subcutaneous tissue had a peculiar gelatinous appearance with fat particles suspended in it. The body cavities contained free fluid, the largest amount being present in the peritoneal cavity (about 20 c.c.).



Fig. 3.—Drawing of the heart of Baby A (Case 2), showing the foramen ovale with overlapping membrane. A, Arrow traversing the foramen ovale; B, left auricle; C, left ventricle; D, right ventricle (hypertrophic).

The heart weighed 30 gm.; the left ventricle was 5 mm. in thickness and the right ventricle 9 mm. The apex of the heart was formed by the right ventricle. The right auricle was not enlarged. Valve circumferences were as follows: tricuspid 3 cm., mitral 2.5 cm., pulmonic 2 cm., and aortic 1.5 cm. The ductus arteriosus measured 1.3 cm. in circumference. The foramen ovale was entirely covered by an overlapping membrane which could be pushed aside from the right auricle to admit a probe 4.5 mm. in diameter. The free edge of the membrane was anterior to the opening between the auricles (Fig. 3). Microscopically, the heart showed hypertrophy of the muscle of both right auricle and right ventricle.

The lungs showed marked edema, congestion, and atelectasis.

The liver weighed 81 gm. and was congested with blood. It showed a moderate amount of iron pigment microscopically, but was otherwise normal.

There was definite cerebral edema; the fluid was bloodtinged because of incomplete lacerations of the dura at the junction of the falx and tentorium.

DISCUSSION

The normal patent foramen ovale and ductus arteriosus of the fetus allow proper division of blood, and proportionate development of both sides of the heart (Fig. 4). Premature closure of the foramen ovale is prone to bring about certain secondary structural abnormalities. It may be assumed that variations in adaptability of different portions of the circulatory system may cause somewhat dissimilar end results. The various possibilities might be as follows: (1) The blood may be detoured through the pulmonary circuit, instead of going directly from the right

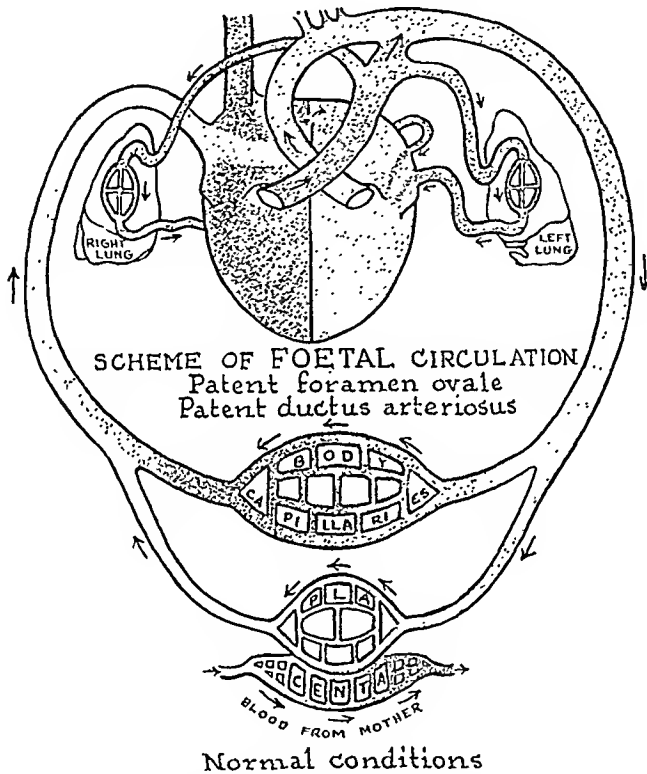


Fig. 4.—Diagram of normal fetal circulation. (From Abbott and Dawson, *Internat. Clin.* 4: 162, 1924).

to the left auricle. If the pulmonary circuit is adequate, or rapidly becomes adequate, a normal amount of blood can reach the left auricle and the heart may thus develop normally. Birth may then be followed by normal development of the infant. (2) If, on the other hand, the pulmonary circuit is not adequate, the excess blood may be shunted to the aorta by way of the ductus arteriosus. If this occurs the ductus may hypertrophy and the left auricle and left ventricle will receive less blood than normal, and so not develop *pari passu* with the right auricle and ventricle, which are being overloaded. (3) In case the fetal pulmonary circuit and ductus arteriosus are both inadequate to carry an increased load, the result will be the same as for any obstruction to free circulation, namely, the development of back pressure. This back pressure may

cause enlargement of the right auricle, as in Case 1, of the right ventricle, as in Case 2, and will eventually hinder the entire circulatory flow from the body and placenta, bringing about stasis and edema of the whole body and the placenta, as well as hydramnios. (4) In some cases it may be possible to maintain the circulation of the fetus in utero well enough to support life. However, in those cases in which the right side of the heart has enlarged disproportionately, the event of birth and the shutting off of the passage of blood through the ductus arteriosus will cause a larger volume of blood to go through the pulmonary circuit than can be pumped by the left side of the heart to the aorta. This will cause stasis in the lungs, with pulmonary edema and inadequate oxygenation, as well as failure of the left side of the heart.

Such an explanation would make clear the mechanism bringing about the syndromes mentioned by Lehman. The infants with edema at birth belong to the group with increasing obstruction during the latter part of fetal life, and the infants who are apparently normal at birth but soon develop cyanosis and die are those whose pulmonary stasis, edema, and left-sided heart failure develop at or after birth, partly because of the closure of the ductus arteriosus. Obviously, too, there might be gradations between these two extremes, as shown by the second case reported above.

The etiology of premature closure of the foramen ovale is probably purely developmental, the causative factor being an abnormality in the timing of the development of the intra-auricular septum. In Maude Abbott's discussion of congenital cardiac disease⁵ the formation of this septum is shown to begin with the septum primum, which grows downward from the upper and posterior wall of the auricle as a sickle-shaped fold. This fold grows toward the ventricular cavity, and there is for a time a communication between the auricles which is known as the ostium primum. This primary membrane becomes very thin, and an opening forms in its upper and posterior part; this secondary opening continues to grow larger as the ostium primum becomes smaller and disappears.

Later, a secondary septum begins to form from the upper wall of the right auricle, grows downward, and comes to overlie the secondary opening in the primary septum, giving it a valvular character and transforming it into the foramen ovale. The ostium in the secondary membrane constitutes the foramen ovale and the valve is formed by the primary membrane. The foramen ovale is normally widely patent in fetal life, usually closes within twelve weeks after birth,⁶ but may show a probe patency throughout the first year.⁷ It may even persist, as a slit, in the adult (14 to 30 per cent of cases⁵). Persistent patency of the foramen ovale is considered to be caused either by pressure or pure growth arrest. The latter seems more likely in view of these cases in which the foramen ovale closes prematurely, since in them the pressure in the right auricle has certainly been increased, but the closure of the foramen has progressed with unusual rapidity.

Patten⁷ stresses the point that congenital defects are as frequently due to overgrowth as to developmental arrest. The cases presented here give evidence in support of this view, as there appears to have been an overgrowth of either the overlapping valve or of the secondary membrane, bringing about an abnormal restriction in the size of the interatrial opening. It is not possible at the present time to determine which structure is primarily involved, as we have no measurements of the size of the secondary ostium in normal cases.

The foramen ovale at birth, in infants whose stage of development is similar to that in the cases presented here, has been found to vary from 7 mm. to 10 mm., as compared to 3 mm. in Case 1, and 4.5 mm. in Case 2. In Case 1, the edema in a stillborn infant denoted inadequate circulation with increasing obstruction during fetal life. In Case 2 the child was born alive, but developed symptoms soon after birth. Therefore, there appears to be a correlation between the degree of reduction in size of the foramen ovale and the extent of the pathologic changes observed in the two infants.

The discovery of cases of early closure of the foramen ovale is obviously possible only in stillborn or newborn infants. The presence of severe general edema should at all times be an indication for careful searching of the heart for an unusually small or absent intra-auricular opening, and for right-sided hypertrophy. Those infants who live for a short time and then become cyanotic and die, and in whom edema is noted, should be carefully examined for a definite right ventricular hypertrophy which can easily be differentiated from the right auricular dilatation so often seen.

SUMMARY

Two cases are presented in which there was partial premature closure of the foramen ovale, associated with fetal anasarca. This condition has been reported only a few times in the literature; all of the cases are similar.

A brief discussion of the mechanism and etiology of the condition is given.

REFERENCES

1. Lehman, E.: Congenital Atresia of the Foramen Ovale, *Am. J. Dis. Child.* 33: 585, 1927.
2. Tait, L.: A Case of General Dropsy in a Foetus, *Tr. Obst. Soc. London* 17: 307, 1875.
3. Osler, Wm.: Cases of Cardiac Abnormalities, *Montreal Gen. Hosp. Reports, Clin. and Path.* 1: 177, 1880.
4. Vieussens, R. (1715), Smith, E. (1846-7), Vernon, H. H. (1856): Mentioned by Lehman (see under reference 1).
5. Abbott, M. E.: Congenital Cardiac Disease, Osler and McCrae's *Modern Medicine IV*, Chapter XXI, p. 612, Philadelphia, 1927, Lea and Febiger.
6. Christie, A.: Normal Closing Time of the Foramen Ovale and the Ductus Arteriosus, *Am. J. Dis. Child.* 40: 323, 1930.
7. Patten, Bradley M.: Developmental Defects at the Foramen Ovale, *Am. J. Path.* 14: 135, 1938.

COARCTATION OF THE AORTA, NONCLINICAL TYPE, ASSOCIATED WITH A CONGENITALLY BICUSPID AORTIC VALVE

A METHOD FOR ITS RECOGNITION, WITH REPORT OF A CASE

PHILLIP HALLOCK, M.D., AND ROBERT HEBBEL, M.D.
MINNEAPOLIS, MINN.

COARCTATION of the aorta, when it presents the classical clinical picture, affords no great difficulty of recognition during life. However, anatomic stenosis just at or below the insertion of the ductus arteriosus or its vestige may exist without hypertension and without the signs upon which the clinical diagnosis of coarctation is usually established. This is the result of the fact that various moderate degrees of narrowing of the isthmus may be present, and it is only in the pronounced grades of stenosis that physical signs may develop. Commonly, slight to even moderate degrees of constriction are missed at autopsy. The recognition of moderate, or "nonclinical," degrees of coarctation is of considerable clinical importance as regards prognosis because, even though the coarctation is not marked, there is still the possibility of associated congenital cardiovascular anomalies and the likelihood that subacute bacterial endocarditis may supervene. Maude Abbott¹ has shown that in approximately 40 per cent of cases coarctation is associated with other congenital anomalies of the heart, the most common being a bicuspid aortic valve, which was present in 25 per cent of the cases.

We are reporting a case of moderate coarctation of the aorta in which the clinical syndrome of coarctation was lacking; the associated anomaly was a congenitally bicuspid valve upon which was superimposed an infectious endocarditis. The correct diagnosis was made during life. In this regard we particularly wish to emphasize the importance of the radiosopic method in the examination of the heart and great vessels because it was by this method that coarctation was recognized in this case. In the left oblique radiosopic position the site of the constriction of the isthmus could be easily visualized (Fig. 1). This position (Fig. 2)^{2a} has been found to be the most satisfactory one from which to study abnormalities of the aortic arch.^{2b}

REPORT OF CASE

E. W., a white woman 31 years of age, a housewife, was admitted to the surgical service Aug. 24, 1937, complaining of weakness, loss of weight, intermittent fever, chills, dull pain in both flanks, and intermittent dysuria. These symptoms had been present since June, 1937.

From the Departments of Medicine and Pathology, University of Minnesota Hospitals, Minneapolis.

Received for publication Sept. 3, 1938.

Patient had given birth to her last baby in February, 1937. This was an uneventful pregnancy. Beginning in the early part of June, 1937, the patient noted that she was losing weight and tiring easily. About this time she suffered an attack of pain in the left flank which persisted, with remissions and exacerbations, for about two weeks. She also noted that she was feverish on occasions and at times had definite chills. Following the initial attack of pain, the patient appeared to improve to some extent except for the persistence of nocturia and weakness. The weakness was so great as to confine her to bed nearly constantly.

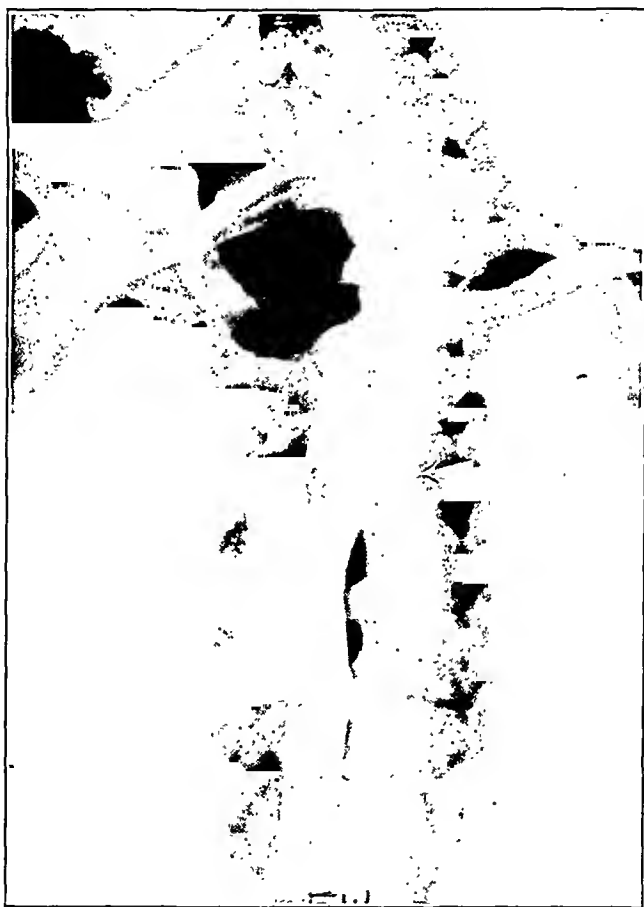


Fig. 1.—Photograph of teleoroentgenogram in the left oblique position. The course of the aorta and the point of stenosis (indicated by arrow) are clearly shown. This point corresponds to the site of constriction shown in Fig. 4a. The opaque shadow lying anterior to, and parallel with, the aorta is the barium-filled esophagus.

Past history.—Patient stated that she had never been strong. Palpitation and tachycardia had been present for a number of years. Because of these symptoms she had consulted a physician five years before, and was told that she had leakage of the heart. There was no history of rheumatic fever, scarlet fever, or diphtheria. She had had five uneventful pregnancies with no resultant difficulties. She had never been short of breath until the onset of her present illness. She had been married for eleven years, had five children who were living and well, and her husband was living and well.

Physical examination.—On admission the temperature was 103°, the pulse rate 90, and the respiratory rate 20. Physical examination revealed an emaciated white

woman lying quietly in bed. There was no apparent distress. There was marked pallor of the skin with evidence of considerable recent loss of weight. The pupils were equal and reacted normally to light and in accommodation. Examination of the eyegrounds showed normal retinal vessels. The teeth were in good condition. The tonsils were enlarged. The thyroid gland was just palpable but not enlarged. There was no cervical adenopathy. A vigorous systolic pulsation and systolic thrill were noted in the suprasternal notch. The heart was not enlarged to percussion. The heart sounds over the apex were clear and slightly accentuated. A systolic murmur, soft and blowing in character, was heard over the apex. Over the aortic area there

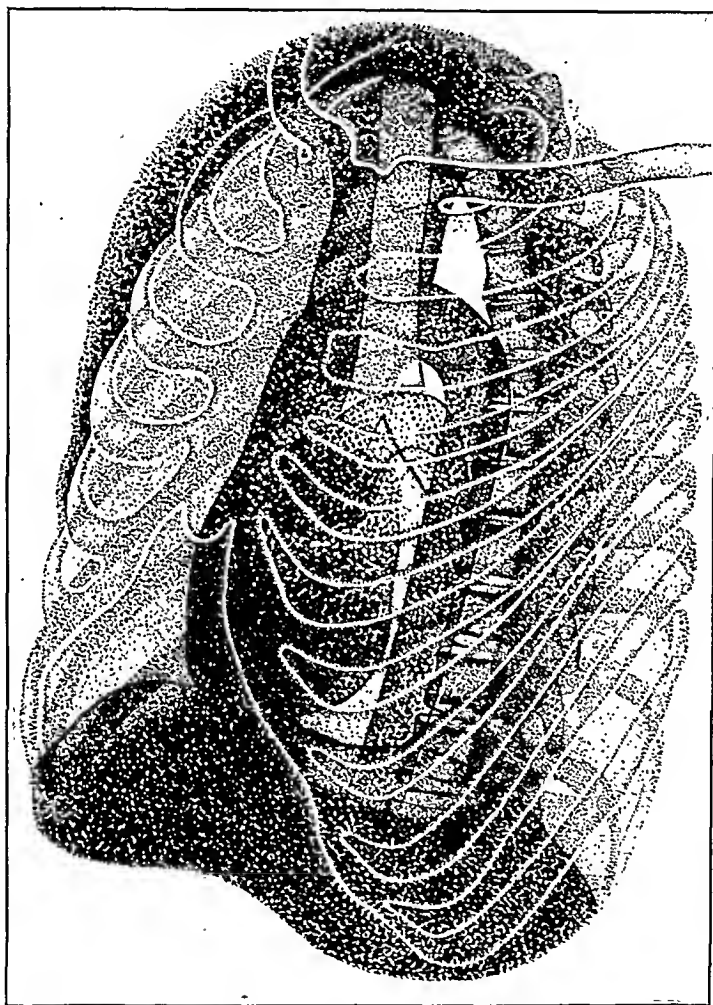


Fig. 2.—Special drawing of normal teleoroentgenogram in the left oblique radioscopic position to show the heart and course of the great vessels (Parkinson and Bedford).

was a low-pitched systolic murmur. The aortic second sound was accentuated. It was succeeded by a high-pitched diastolic murmur. The diastolic murmur became more pronounced when the stethoscope was moved across the left border of the sternum at the level of the third rib. It could also be heard, but with lessened intensity, along the left sternal border as low as the level of the fourth intercostal space. The blood pressure in the left arm was 104/70, in the right arm 100/62, in the left leg 108/66, and in the right leg 110/62. The radial pulses were equal. The femoral, popliteal and dorsalis pedis pulses were of normal amplitude. Examination of the lungs was negative. Abdominal examination revealed no masses. There was

tenderness to pressure over the left upper quadrant. Pelvic examination revealed a relaxed pelvic floor, a first-degree retroversion of the uterus, and a mucopurulent discharge from the cervix. The extremities were negative. There was no edema. There was neither cyanosis nor petechiae. Neurological examination was negative. No signs of collateral circulation were found.

Laboratory Data.—On admission the urine contained numerous erythrocytes and occasional leucocytes. The hemoglobin was 67 per cent. The erythrocyte count was 3,300,000 and the leucocyte count 13,600, of which 85 per cent were polymorphonuclear cells and 15 per cent lymphocytes. The blood Wassermann reaction was negative.

Fluoroscopic examination of the heart and lungs revealed the following: The lung fields were clear. The heart was within normal limits as to size, shape, and position. The arch of the aorta was markedly elongated and dilated, extending upward above the sternal angle to the root of the neck. The aortic impression on the barium-filled esophagus was particularly marked. With the patient in the left oblique position the descending portion of the arch of the aorta could be clearly followed into the shadow of the spine, extending down to a point about at the level of the pulmonary artery. At this level the aorta became distinctly narrowed as though it were surrounded by a constricting band (Fig. 2). Distal to this constriction the arch of the aorta could be seen to widen out again. Scalloping of the inferior borders of the ribs (Roesler's sign) was not present.

The electrocardiogram showed normal rhythm, a heart rate of 96, left axis deviation, a diphasic T_3 , and a normal fourth lead. In view of the radiosopic examination, normal blood pressure readings in the upper and lower extremities, the absence of signs of collateral circulation, and the presence of an aortic diastolic murmur, a diagnosis of partial coarctation of the aorta, associated with a bicuspid aortic valve, was made.

The patient was observed in the hospital for a period of ten days, during which time there was no appreciable change in the findings. She was discharged against advice Sept. 8, 1937. She was readmitted to the medical service Nov. 8, 1937. Her history during the interval was as follows: Aside from increasing weakness, she felt fairly well until the morning of Sept. 31, when she developed a severe stabbing pain just to the left of the sternum. The pain radiated to the left shoulder and down the left arm. It appeared suddenly and persisted for several hours, after which it abated and remained as a dull pain in the left chest for several days. On the morning of October 7, while lying in bed, she developed another similar attack of pain. The attack persisted until the night of the same day. The next day she still complained of pain in her left chest and left upper quadrant. Since her previous admission she stated that she had had fever but no chills.

Physical examination on this admission revealed fresh petechiae in both conjunctivae. Examination of the eyegrounds revealed flame-shaped hemorrhages in both fundi and slight choking of both discs. There was a marked pallor of the lips and mucous membranes. The cardiac findings were the same as on the previous admission except that a presystolic murmur was present over the apex. Neither the spleen nor the liver was palpable. A skin test with the nucleoprotein fraction of the nonhemolytic streptococcus was negative on Nov. 11, 1937. On this same day more petechiae appeared in the conjunctivae. The spleen was now palpable and markedly tender. A splenic infarct was suspected. The blood culture was positive for non-hemolytic streptococci, showing one hundred colonics per cubic centimeter. This fact that the patient now had obvious bacterial endocarditis strengthened the diagnosis of a bicuspid aortic valve. The urine on this admission showed a specific gravity of 1.012; it contained albumin (graded 1+), and many leucocytes. The hemoglobin was 48 per cent, the erythrocyte count 3,300,000, and the leucocyte count 11,000. The differential leucocyte count showed 87 per cent polymorphonuclear cells,

12 per cent lymphocytes, and 1 per cent monocytes. The other laboratory findings were not significantly altered. The radioscopic findings of the heart were essentially the same as those previously noted.

Course of the Disease.—Marked tenderness developed over the splenic area and there was tenderness to pressure over the sternum. The patient was given large doses of sulfanilamide without improvement in her condition. The blood culture remained positive. The temperature was septic in type, ranging up to 102° F., with a pulse rate varying between 90 and 120. On Nov. 21, 1937, râles appeared in the right chest below the scapula. Cyanosis developed and the blood pressure dropped. Dyspnea and respiratory distress increased. The patient expired Nov. 27, 1937.



Fig. 3.—Interior view of the heart, showing the left ventricle and the bicuspid aortic valve. The valve was opened through the left posterior commissure, so that as seen in the photograph, the posterior cusp is to the right, the conjoined cusp to the left. The raphe is indicated by the arrow at *a*.

The pertinent autopsy findings were as follows: There was mild pitting edema of the feet and ankles. Each pleural cavity contained a liter of clear fluid and there were 250 c.c. of a similar fluid in the pericardial sac. The lungs were moderately congested and there was a partial atelectasis of the lower lobes. The spleen weighed 500 gm., presented scattered yellow infarcts and a single suppurative infarct 5 cm. in diameter, and showed, microscopically, subacute splenitis. There was a moderately severe passive congestion of the liver. The kidneys presented scattered contracted infarcts and, microscopically, a minimal embolic glomerulitis.

The heart (including the attached portion of the aortic arch) weighed 330 gm. and was not enlarged. The epicardium and myocardium showed nothing of note. The endocardium of the right atrium, right ventricle, and left atrium was normal. The left ventricular endocardium, except for a group of minute, friable vegetations just below the right posterior commissure, was normal. The pulmonary, tricuspid, and mitral valves were normal. There was a bicuspid aortic valve, the free margins of which were covered with and distorted by large, friable vegetations. The cusps showed no thickening near their attached margins and there was no indentation of the central portion of the combined cusp at the point of its attachment. The left posterior commissure was normal; the right posterior commissure was involved in the infective process but there was no evidence of previous fusion. The position of the right-left commissure was occupied by a low raphe (Fig. 3a), the smooth, cord-like free margin of which became bifid as it approached and merged with the cusp. Beneath its cordlike margin the raphe was thin and delicate. The breadth of the posterior cusp at the level of its commissures was 25 mm., and that of the combined cusp was 32 mm.; the raphe was equidistant from its extremities. The aorta, in the sinus behind the posterior cusp and at a point midway between its commissures, presented small mycotic aneurysms. The coronary orifices and coronary vessels were normal.

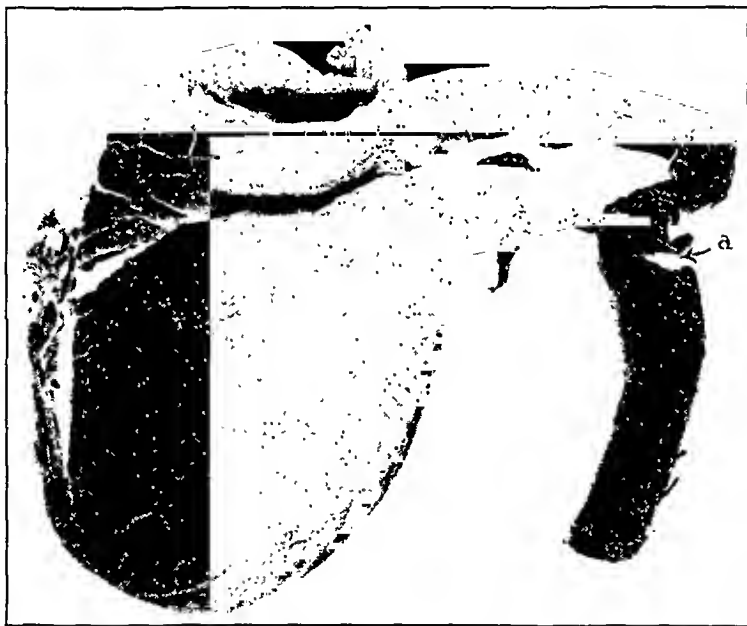


Fig. 4.—Photograph of heart and aorta showing the point of constriction (*a*) just below the insertion of the obliterated ductus arteriosus.

Of the branches of the aorta the left common carotid and left subclavian were distinctly larger than the innominate. The lumen of the aorta between the sites of origin of the innominate and the left common carotid was diffusely narrowed. At the site of attachment of a cordlike obliterated ductus arteriosus the aorta presented a distinct notching which was most marked on its free border (Fig. 4a). The lumen at this point was acutely constricted. The diameters of various points of the aortic arch were as follows: root, 1.7 cm.; between innominate and left common carotid, 1.2 cm.; between left common carotid and left subclavian, 1.5 cm.; site of constriction, 1.2 cm.; 3 cm. distal to constriction, 1.7 cm. The segmental branches of the aorta and the internal mammary arteries were normal.

Microscopic sections of the valve rings and myocardium showed no direct evidence of previous rheumatic infection. The myocardium showed areas of diffuse and focal inflammation characterized by polymorphonuclear exudate, as well as a few areas of scarring. The aortic valve presented the typical appearance of subacute bacterial endocarditis. Longitudinal sections at the site of the raphe of the conjoined aortic cusp showed absence of the normal inversion of the aortic wedge.

DISCUSSION

All grades of stenosis of the isthmus of the aorta may occur, varying from complete obliteration to one which is so slight that it may be overlooked on careful post-mortem examination. In the 200 cases of coarctation analyzed by Abbott¹ there were forty-seven in which the arch of the aorta was completely obliterated, 108 of extreme narrowing in which the diameter at the site of the stenosis did not exceed 6 mm., and forty-five in which the stenosis was of a moderate grade approximating one-third the size of the normal caliber of the aorta. The case reported here falls in the last series, which may be considered as a nonclinical group.

The importance of recognizing cases in this group extends beyond mere academic interest. Hitherto, the diagnosis in this nonclinical group has been made only at necropsy. Death in these cases may occur from spontaneous rupture of the aorta, from bacterial aortitis invading the area of coarctation, or from subacute bacterial endocarditis with vegetations on the bicuspid aortic valve which is so frequently associated with coarctation. From a practical viewpoint nonclinical degrees of coarctation are therefore of definite prognostic significance and attempts should be made to recognize them during life. Inasmuch as the clinical features, such as arterial hypertension and signs of collateral circulation, are absent in these cases, the diagnosis can only be arrived at by direct radiosopic examination of the aortic arch, which is best studied in the left oblique radiosopic position. The observation which called our attention to the existence of some abnormality of the aortic arch was the presence of a systolic pulsation and thrill in the suprasternal notch. These signs were perceptible, as subsequent radiosopic examination showed, because the aortic arch occupied an unusually high position.

The bicuspid aortic valve with two distinct cusps is readily accepted as congenital. However, when the valve presents a conjoined segment with a raphe, supportive evidence is required before it may be accepted as a case of developmental arrest.¹ For this type of case the macroscopic criteria of Osler³ and the microscopic criteria of Lewis and Grant⁴ must be fulfilled. We believe that the bicuspid aortic valve in the case here reported was of congenital origin. In the first place, it was associated with a developmental defect of the aorta. The macroscopic criteria of Osler, except insofar as the infective process prevents their demonstration, were fulfilled. Microscopically, the absence of the normal inversion

of the aortic wedge^{4, 5} at the site of the raphe satisfied that portion of the criteria of Lewis and Grant. The choice of longitudinal sections precluded the demonstration of the continuity of the fibers of the aortic media across the raphe. Furthermore, because of the fact that there was no microscopic evidence of previous rheumatic infection⁶ and, because the existing inflammatory changes were entirely those which may occur during the course of subacute bacterial endocarditis, an inflammatory origin of the bicuspid condition of the valve may be excluded.

CONCLUSIONS

A case of nonclinical coarctation of the aorta associated with a congenitally bicuspid aortic valve is reported, the recognition of which was made possible by radioscopic examination. Because of the frequent association with other congenital vascular anomalies which are of a serious nature, the recognition of nonclinical coarctation is of considerable prognostic importance.

REFERENCES

1. Abbott, M. E.: Coarctation of the Aorta of the Adult Type, Part II. A Statistical Study and Historical Retrospect of 200 Recorded Cases, with Autopsy, of Stenosis or Obliteration of the Descending Arch in Subjects above the Age of Two Years, *AM. HEART J.* 3: 392, 574, 1928.
- 2a. Parkinson, J., and Bedford, D. E.: The Aortic Triangle. A Radiologic Landmark in the Left (or II) Oblique Position, *Lancet* 2: 909, 1936.
- 2b. Hallock, Phillip: Enlargement of the Heart, *Minnesota Med.* 21: 303, 1938.
3. Osler, William: The Bicuspid Condition of the Aortic Valves, *Tr. A. Am. Physicians* 1: 185, 1886.
4. Lewis, Thomas, and Grant, R. T.: Observations Relating to Subacute Infective Endocarditis, Part II, On Bicuspid Aortic Valves, *Heart* 10: 31, 1923.
5. Gross, Louis, and Kugel, M. A.: Topographic Anatomy and Histology of the Valves in the Human Heart, *Am. J. Path.* 7: 445, 1931.
6. Gross, Louis: So-called Congenital Bicuspid Aortic Valve, *Arch. Path.* 23: 350, 1937.

NONRHEUMATIC CALCIFIC AORTIC STENOSIS

CHARLES K. FRIEDBERG, M.D., AND ARTHUR R. SOHVAL, M.D.
NEW YORK, N. Y.

SINCE the publication of Christian's¹ paper, in 1931, we have identified calcific aortic stenosis as a distinct clinical entity with characteristic, interesting manifestations. As a result of a number of recent publications, we now recognize the frequency and importance of this disease.²⁻⁷ The clinical diagnosis has been greatly facilitated by a growing acquaintance with its distinctive symptomatology, by broadening of the previously rigid diagnostic criteria of aortic stenosis, and by demonstrating the characteristic roentgenographic appearance of the valves.

Apart from the endeavor to improve the means of making the clinical diagnosis, calcific aortic stenosis still offers many problems of interest. A lively discussion has been engendered by uncertainty as to its etiology and as to the exact pathogenesis of its distinctive manifestations, namely, angina pectoris, disturbances in cardiac conduction, syncope, and sudden death. The purpose of this study was primarily to review the clinical features in a group of autopsy cases of calcific aortic stenosis in which one of us had previously excluded the possibility of a rheumatic etiology.⁸ As a corollary we attempted to determine whether it was clinically possible to differentiate the rheumatic from the nonrheumatic cases. As a result of this study we are proposing an explanation, compatible with physiologic, clinical, and anatomic observations, for the occurrence in this disease of angina pectoris, syncope, electrocardiographic evidences of conduction disturbances, and sudden death.

ETIOLOGY AND PATHOLOGY OF CALCIFIC AORTIC STENOSIS

It has long been known that calcific aortic stenosis may be the result of rheumatic valvular disease. Mönckeberg⁹ was clearly aware of this when, in 1904, he segregated a group of cases of calcific aortic stenosis in which he believed that the lesion was due, not to rheumatic fever, but to primary sclerotic and calcific degeneration. Since that time it has been erroneously assumed that Mönckeberg and others who think that there is a primary degenerative form of calcific aortic stenosis believe that the disease is noninflammatory in all cases. The reports of Christian,¹ Clawson and his co-workers,¹⁰ and others, as well as our own observations, indicate clearly that rheumatic fever is the cause in the majority, perhaps in the preponderant majority, of

From the Medical Services, The Mount Sinai Hospital, New York.
Received for publication Oct. 3, 1938.

cases of calcific aortic stenosis. There is a dispute only as to whether, in addition to the rheumatic cases, there is also a nonrheumatic, primarily degenerative, calcific aortic stenosis. While various statistical studies of the etiology of this disease point out the importance of rheumatic fever, they do not preclude the possibility of a primary degenerative process in some cases. Detailed histopathologic investigation offers direct evidence that in certain cases the lesion is due to primary sclerocalcific disease and that this lesion can be distinguished microscopically from those caused by rheumatic fever.⁸

In a recent comprehensive review of calcific aortic valvular disease, Clawson and his co-workers¹⁰ concluded that it was invariably due to rheumatic infection. Their conclusion was based essentially on the following observations: (1) A rheumatic history, adherent pericardium, and Aschoff bodies were found almost as frequently in association with calcified aortic stenosis as with other old valvular lesions which were known to be caused by rheumatic fever; (2) macroscopic study of the aortic valves did not indicate that there is a distinctive form of primary sclerocalcific disease; (3) microscopic examination of these valves revealed what was apparently an inflammatory reaction, and the presence of blood vessels, in a high percentage of cases.

As already stated, this evidence merely indicates that rheumatic fever is a frequent cause of calcific aortic stenosis but it does not preclude the existence of a nonrheumatic form of this ailment. Clawson, et al.,¹⁰ point out that a history of rheumatic fever was obtained in 35 per cent of the cases of calcified aortic nodular sclerosis, as compared with 41 per cent in cases in which there were other healed (probably rheumatic) valvular lesions, from which he concluded that the lesions in both groups were of rheumatic origin. Since in the great majority of cases of calcific aortic stenosis the etiology is admittedly rheumatic, the presence of a relatively small group of nonrheumatic cases would have but little effect in diminishing the percentage of positive rheumatic histories for the entire calcific group. Thus, a 6 per cent difference between the incidence of positive rheumatic histories in the more definitely rheumatic (healed) valvular group and the incidence of positive rheumatic histories in the group of 200 cases of calcific aortic stenosis might represent as many as 30 nonrheumatic cases.

Clawson, et al.,¹⁰ stressed the fact that the age at death of individuals with aortic valvular disease did not differ essentially from that of individuals with definitely rheumatic (healed) valvular defects. This similarity would be significant if the age at death of individuals with definitely rheumatic valvular defects was compared with that of individuals who had calcific aortic stenosis without associated disease of the mitral valve. For, since mitral valvular disease is usually due to rheumatic fever, nonrheumatic calcific aortic stenosis is most likely

to be found in individuals without mitral lesions. But an analysis of the data in the report of Clawson, et al., reveals that whereas 54 per cent of the individuals in whom calcific aortic disease was associated with mitral lesions (i.e., an essentially rheumatic group) died before the age of 50 years, only 27 per cent of those with pure calcific aortic disease (sometimes nonrheumatic) died before that age. If we were to exclude some of the very young patients, who were undoubtedly rheumatic, from this pure aortic group, the disparity in age at death between those with nonrheumatic and those with rheumatic calcific aortic valvular disease would be even greater. If the viewpoint of Clawson, et al., that rheumatic fever is the only cause of calcific aortic stenosis were correct, the average age at death of individuals with rheumatic stenosis, as found by these authors, would be much higher than that of individuals with any other rheumatic valvular lesion, a conclusion which is incompatible with the numerous studies of the prognosis of rheumatic heart disease.

The data on sex presented by Clawson and his co-workers¹⁰ also appear to affirm rather than negate the existence of a nonrheumatic type of calcific aortic valvular disease. In their 200 cases there were 165 males and 35 females, a proportion similar to that reported by other observers. This plurality of males is quite disproportionate to the distribution of sex in patients with definitely rheumatic valvular defects.

According to the data of Clawson, et al., there were 111 instances of pure calcific aortic stenosis without mitral lesions. If the aortic defect in all of these cases were due to rheumatic fever, calcific aortic stenosis would be the commonest rheumatic valvular lesion. But this assumption contradicts numerous observations indicating that rheumatic fever attacks the mitral valve most frequently.

In the same series, the location of the calcified nodules in the aortic cusps also sheds light on the etiology of the disease. In rheumatic calcific aortic disease the calcific nodules occur first and predominantly on the ventricular surface of the valve, while in the nonrheumatic degenerative cases they occur on the aortic surface. When the calcification is advanced and widespread, both surfaces may be affected. Clawson, et al., report that in 11 per cent of 106 cases there were calcified nodules on the aortic surface only. This 11 per cent appears to us to represent the minimum percentage of definite nonrheumatic cases of calcific aortic disease, but, in addition, there must have been other nonrheumatic cases in which the calcification had spread to both surfaces of the valve.

An objection is sometimes raised to the possibility of a nonrheumatic calcific aortic stenosis on the ground that the aorta is not as calcified as the aortic valve, but this objection is no more valid than to doubt the primary degenerative nature of calcification and sclerosis

of the aorta in cases in which there is no corresponding calcific sclerosis of the aortic valve. It must be admitted merely that it is not completely understood why excessive amounts of lime are deposited in one site rather than in another. In some instances, the absence of arteriosclerosis at the base of the aorta is due most probably to the protective effect of the stenosis of the aortic orifice.

The histologic studies of Mönckeberg,⁹ Geerling,¹¹ and Giese¹² have already indicated certain characteristic pathologic features of primary calcific aortic stenosis which distinguish this lesion from that secondary to rheumatic endocarditis. Briefly, the following features were observed: (1) Calcification began and was most extensive in the sinus pocket and base of the valve, and progressed thence to the free margin. In rheumatic valves, the calcification began and was most extensive in the distal third of the valve. (2) The calcific process affected predominantly the fibrous layer of the valve cusp on the aortic side of the leaflet. Calcification in rheumatic valves occurred predominantly in the spongiosa and ventricularis layers on the ventricular aspect of the aortic cusp.

More recently, Sohval and Gross⁸ not only confirmed these distinctions, but were able to eliminate definitely the possibility of rheumatic infection in a group of cases in which they concluded that the lesion was primary calcific sclerosis of the aortic valves. As a result of extensive studies in the pathology of rheumatic fever, Gross and his co-workers¹³ were able to demonstrate that even in cases of old, healed, rheumatic valvulitis, definite stigmas of rheumatic infection could be found in a variety of strategic sites, such as the left auricle, the valve rings, the valve cusps, the pericardium, etc. Thus, in nineteen instances of gross, polyvalvular, healed, rheumatic disease studied by Sohval and Gross⁸ there was a very high incidence of widespread, microscopic, rheumatic lesions. Similarly, in thirteen other hearts, in which gross examination showed a healed rheumatic deformity of a single valve, histologic examination revealed a high incidence of rheumatic lesions not only in the grossly affected valve but also in the numerous other cardiac sites in which rheumatic lesions are usually found. It appeared from these histologic studies that pure monovalvular rheumatic disease was probably a rarity. On the other hand, in fifteen hearts with calcific aortic stenosis which resembled microscopically and macroscopically the primary degenerative lesion described by Mönckeberg,⁹ detailed microscopic study of the various cardiac sites failed to reveal the lesions found in the rheumatic hearts. As a result of these studies, Sohval and Gross believed that they had definitely demonstrated that nonrheumatic calcific aortic stenosis exists, and had indicated how this form could be differentiated histopathologically from rheumatic aortic disease with superimposed calcification.

TABLE I

NO.	AGE	SEX	ANGINA PECTORIS	CONDUCTION DEFECT	SUDDEN DEATH	SYSTOLIC MURMUR	DIASTOLIC MURMUR	THRILL	B.P.	CORONARY NARROWING	MYO- CARDIAL INFARCT	HEART WEIGHT
Patients with failure:												
1.	46	M	+	Arb. block	-	Apex and base +	+	-	100/80	+++ +++ +++	-	-
2.	77	F	+	-	-	Apex +	-	-	145/70	Old occlusion ACO Old occlusion	aneurysm	510 gm.
3.	72	F	+	-	-	Apex and base +	+	-	99/61	Old occlusion	-	550
4.	68	F	-	LBBB	+	Generalized +	-	-	130/72	+++	-	-
5.	62	M	+	PR = .24 LBBB	-	Apex and base Musical +	-	+	-	+++	-	-
6.	61	M	+	-	-	Apex and base Rough +	+	-	130/70	-	-	470
Patients without failure (or circulatory symptoms):												
7.	43	F	-	-	-	-	-	-	104/60	-	-	460
8.	60	F	-	-	-	-	-	-	-	-	-	350
9.	64	F	-	-	-	-	-	-	-	-	-	-
10.	74	M	+	-	-	Apex and base +	-	-	160/90	+++ LAD	-	-
11.	48	M	-	-	-	-	-	-	120/80	-	-	325
Patients with failure and syphilitic aortitis:												
12.	48	M	+	-	+	Apex and base Rough +	+	-	134/35	+++	-	-
13.	50	M	-	-	-	Apex and base +	+	-	190/72	+++	+	710
14.	66	M	+	-	+	Apex and base +	+	-	130/60	+++	-	700
15.	30	M	+	Arb. block	+	Generalized +	+	+	300/38	-	+	1300

ACO = acute coronary occlusion.

LAD = left anterior descending coronary.

Arb. block = intraventricular conduction defect.

LBBB = left bundle branch block.

PR = PR interval.

CLINICAL FEATURES

This report presents the clinical features in the fifteen examples of calcific aortic stenosis studied histologically by Sohval and Gross.⁸ In eleven of the cases there was pure calcific aortic stenosis, without associated syphilitic, rheumatic, or other infectious lesions of the heart and valves. In four cases there was a concomitant syphilitic aortitis and aortic insufficiency. The essential data in all of the cases will be found in Table I. Seven representative cases are presented below.

The clinical manifestations in these nonrheumatic cases did not differ essentially from those in cases of calcific aortic stenosis which have been described by several observers who did not attempt to segregate the rheumatic from the nonrheumatic cases. The fifteen cases studied fell into three groups. In the first group, consisting of six cases (of which Cases 1 to 5, inclusive, are presented in detail), the patients were admitted to the hospital because of symptoms of cardiac failure. In the second group, consisting of five cases (of which Case 11 is presented as an example), the existence of the valvular lesion was not suspected and there were neither cardiac failure nor other symptoms usually associated with the disease, although in one case the possibility of a congenital cardiac lesion was considered because of the presence of an unusual murmur. In the third group, consisting of four cases (illustrated by Case 15), cardiac failure was as predominant a feature as in the first group, but these cases were segregated because of coexisting syphilitic aortic valvular disease.

The characteristic features of calcific aortic stenosis were usually found in the group of patients who were hospitalized because of cardiac failure. These features included dizziness or syncope, angina pectoris, disturbances in cardiac conduction, and sudden death. The hearts in this group presented the severest degree of aortic stenosis and had suffered the greatest strain. In consequence, these hearts had undergone conspicuous hypertrophy and weighed more than those in the other groups.

The incidence of the above-mentioned symptoms is probably higher than would appear from the case reports. Instances of sudden death from calcific aortic stenosis are more likely to appear in coroners' statistics than in the hospital records of individuals admitted because of symptoms of cardiac failure. Certain symptoms of the disease are not likely to be mentioned by a patient who is concerned with the more distressing evidences of cardiac failure. Thus, mention of dizziness, syncope, and angina pectoris is elicited only by specific questioning. Since in most of the cases here reported the presence of calcific aortic stenosis was not suspected ante mortem, specific inquiry as to the occurrence of dizziness and syncope was probably not made. These symptoms will be discussed in detail following the case reports.

Symptoms of cardiac failure may be the first subjective manifestations of the disease. Cardiac failure was the commonest cause of death. The symptoms appeared in an almost uniform sequence. First, there were evidences of left-sided heart failure. Exertional dyspnea was usually the earliest symptom. This was often present for many years before any other symptoms developed. Later, the patients suffered attacks of paroxysmal dyspnea, which usually occurred at night. Eventually, signs of right-sided heart failure appeared, such as peripheral edema, enlargement of the liver, and other evidences of venous engorgement. The duration of life after the onset of right-sided heart failure was brief, rarely exceeding six months.

CASE REPORTS

CASE 1.—F. M., 60-68, a salesman, aged 46 years, entered the hospital because he had had shortness of breath for two weeks. He had never had rheumatic fever. For many years he had experienced pain in the left scapula. For three years he had had attacks of dyspnea on exertion, with asthmatic symptoms, which were ascribed to a neurosis. Three years before admission he suddenly became dizzy, weak, and nauseated. The symptoms subsided after two hours. Eight months later he suffered a similar attack, in which "everything went black for a few hours." Two weeks before admission he had another attack, characterized by sharp epigastric and chest pain, severe dyspnea, and swelling of the ankles.

Examination revealed diffuse râles throughout both lungs and a small area of consolidation at the base of the right lung. The heart was enlarged toward the left. There were a systolic and a diastolic murmur at the apex of the heart, a systolic murmur over the aortic area, and a diastolic murmur in the third left intercostal space. The liver was enlarged; its lower edge was felt 8 cm. below the costal margin. There was slight edema of the ankles. The blood pressure was 100/80. An electrocardiogram showed low voltage in all leads, and thickening and widening of the QRS complexes indicating arborization block. A roentgenogram of the chest showed marked hypertrophy and dilatation of the left ventricle, and moderate enlargement of the right side of the heart. There was diffuse congestion in the lungs.

The *clinical diagnosis* was coronary artery disease with congestion of the lungs. Despite bed rest and digitalization, the patient developed increasing edema of the feet and over the sacrum. He complained of severe precordial, abdominal, and left scapular pain. After five days he began to expectorate bloody sputum. He died nine days after admission.

Post-mortem examination revealed generalized arteriosclerosis; calcific aortic stenosis and insufficiency; cardiac hypertrophy and dilatation; chronic passive congestion of the lungs, liver, spleen, and kidneys; ascites; pulmonary emboli, and infarction of the right lung.

The heart weighed 500 gm. The arch of the aorta was slightly dilated and had lost its elasticity. The right coronary orifice was narrowed. Both coronary arteries showed thickening of the wall, loss of elasticity, and irregular calcified atheromatous plaques.

CASE 2.—E. B., 301521, a woman, 77 years of age, was admitted to the hospital because for one year she had experienced progressive dyspnea, palpitation, and cardiac pain. The pain radiated from the precordium to the left shoulder and arm. In the preceding month she had become orthopneic and had noted edema of the legs.

Examination revealed an acutely ill woman, who was dyspneic, orthopneic, and cyanotic. There were signs of fluid at the base of the left lung. The heart was markedly enlarged to the left and right. There was a soft blowing systolic murmur over the apex of the heart. The pulse was rapid, thready, and barely perceptible. The liver was enlarged and tender. The lower extremities were very edematous. The blood pressure was 145/70.

The *clinical diagnosis* was coronary artery disease and myocardial insufficiency. The electrocardiographic changes (left axis deviation and displacement of the RT segments in Leads I and III) were regarded as compatible with hypertension and myocardial involvement. The patient improved after rest in bed and treatment with morphine and digitalis. Four days after admission she died in an attack of pulmonary edema.

Post-mortem examination revealed generalized arteriosclerosis; calcified aortic stenosis and insufficiency; chronic passive congestion of the liver, spleen, and kidneys; and renal arteriosclerosis.

The heart weighed 510 gm., both ventricles being hypertrophied and dilated. The right coronary orifice was reduced to pin-point size by atheroma. The left anterior descending branch was almost completely calcified; there was an old closure of the vessel near the apex. In the myocardium near the apex there was an old fibrotic area whose endocardial surface was covered by a thrombus. The myocardium was studded with yellow flecks. The aorta was inelastic and showed severe arteriosclerosis.

CASE 3.—C. W., 312969, a woman, aged 72 years, who was known to have had a cardiac murmur for thirty-five years, had long complained of palpitation and dyspnea on exertion but had always been able to do strenuous work. For fifteen years she had experienced precordial pain and epigastric distress. In the preceding two years her dyspnea had increased greatly, and orthopnea and edema of the ankles had appeared. For the preceding three weeks these symptoms had become intensified, and she had developed severe precordial oppression and a hacking cough.

Examination revealed signs of left- and right-sided heart failure, including hydrothorax and ascites. The heart sounds were of poor quality. There was a soft systolic murmur at the apex and the base. At the left of the sternum there was a diastolic murmur which later disappeared. The patient's blood pressure varied between 110/70 and 88/52. An electrocardiogram revealed left axis deviation and a negative T in Lead I. The urine contained a large amount of albumin and many red and white blood cells.

The *clinical diagnosis* on admission was coronary artery disease, rheumatic mitral stenosis, aortic insufficiency, and myocardial failure. The patient's condition grew progressively worse. Her blood urea nitrogen mounted to 90 mg. per 100 c.c. and she died three weeks after admission.

Post-mortem examination revealed extreme calcific aortic stenosis; calcification of the mitral ring; generalized cardiac hypertrophy and dilatation; pulmonary infarction of recent origin; necrotizing cystitis; chronic passive congestion of the viscera.

The heart weighed 550 gm. The aorta was smooth. The left anterior descending artery was entirely occluded by a fresh thrombus. The left coronary artery and the right posterior descending coronary artery were calcified and narrowed, and each showed evidence of an old occlusion. There was extensive myomalacia and endocardial thrombosis of the left ventricle.

CASE 4.—I. R., 335867, a woman, aged 68 years, had a twenty-five-year history of asthma and chronic bronchitis. Four years before admission she had had a cerebral thrombosis with resultant hemiplegia. Five days after catching a cold she went to bed because of weakness, dyspnea, and orthopnea.

Examination revealed an acutely ill, dyspneic, orthopneic, and cyanotic woman. There were diffuse râles throughout the lungs. There was a harsh systolic murmur all over the precordium, most intense at the base. The blood pressure was 138/70, and later 122/74. The total leucocyte count was 18,000, of which 90 per cent were polymorphonuclear leucocytes. An electrocardiogram revealed left bundle branch block.

The *clinical diagnosis* was bronchopneumonia, chronic bronchitis, emphysema, and cardiac failure. The patient ran a febrile course and died four days after admission.

Post-mortem examination revealed calcific aortic stenosis and calcification of the mitral ring; diffuse bronchopneumonia, chronic bronchitis and emphysema; cylindrical bronchiectasis; nephrocirrhosis atherosclerotica lenta progressa; chronic passive congestion of the viscera; subacute splenic swelling.

The heart weighed 550 gm. The coronary arteries and their branches showed marked atherosclerosis and narrowing. The aorta revealed severe atherosclerosis and dilatation of its arch.

CASE 5.—L. S., 346315, a laborer, aged 62 years, had suffered weakness, precordial pain, substernal oppression, dyspnea, and orthopnea for one and a half years. For six months he had been confined to bed because of swelling of the legs and abdomen. He had had nosebleeds frequently, and bloody stools for four weeks. On the day of admission he had coughed up bloodtinged sputum.

Examination revealed an emaciated old man who was somewhat dyspneic and cyanotic. The heart was enlarged. There were a systolic thrill and a harsh systolic murmur in the aortic area. At the lower end of the sternum and at the apex there was a musical systolic murmur. There was extreme edema of the lower extremities and over the sacrum. There was free fluid in the abdominal cavity. The blood pressure was 94/54. A roentgenogram of the chest showed hypertrophy and dilatation of the left ventricle. An electrocardiogram revealed left bundle branch block. The PR interval measured 0.24 second.

The *clinical diagnosis* was cirrhosis of the liver, coronary artery disease, and atherosclerotic calcification of the aortic valve. Despite abdominal paracenteses and treatment with mercurial diuretics, the patient became progressively worse and died eight days after admission.

Post-mortem examination revealed calcific aortic stenosis; primary carcinoma of the liver with extension into the portal vein and inferior vena cava; cirrhosis of the liver.

The heart weighed 460 gm. There were moderate sclerosis and narrowing of the coronary arteries.

CASE 11.—I. W., 373542, a tailor, aged 48 years, had had hematuria, frequency of urination, and nocturia for two years, during which time he had lost 18 pounds. There was no history of rheumatic fever or cardiac disease.

Examination revealed a chronically ill, emaciated man. His heart was somewhat enlarged. There was a loud, blowing, systolic murmur over the entire precordium, radiating to the back. On rectal examination, an egg-sized mass was felt just above the prostate. The blood pressure was 120/80.

The *clinical diagnosis* was neoplasm of the bladder, congenital heart disease, and pulmonary emphysema. Cystoscopy disclosed a papillary neoplasm involving the trigone. An electrocardiogram showed slurring of the QRS complexes. Partial resection of the bladder was performed, several remaining papillomatous tumors were electrocoagulated, and the right ureter was reimplanted. Osteomyelitis of the pubis and a suprapubic sinus developed, after which the patient ran a febrile course for many months and finally succumbed.

Post-mortem examination revealed a necrotizing cystitis; bilateral ureteral calculi and ascending ureteropyelonephritis; calcific aortic stenosis; hypertrophy of both ventricles.

The heart weighed only 325 gm. despite the apparent hypertrophy of the ventricles. The coronary ostia were normally patent. The coronary vessels were slightly thickened, but there was no diminution in the caliber of their lumina.

CASE 15.—M. S., 331428, was a man, aged 30 years, whose father had died of aortitis and whose mother had had an aortic aneurysm. Three years before admission he had had ulceration of both eyes. At that time his blood gave a positive Wassermann reaction. Thereafter he had suffered increasing weakness, dyspnea on exertion, and attacks of angina pectoris. For one month he had had insomnia, orthopnea, edema of the ankles, and a productive cough.

Examination revealed bilateral corneal opacities, signs of fluid in the right pleural cavity, and extreme enlargement of the heart. There was a systolic thrill over the aortic area and at the apex of the heart. A systolic and a diastolic murmur were heard all over the precordium. There was a Corrigan pulse. The liver was enlarged and tender. There was slight peripheral edema. The blood pressure was 300/38.

The *clinical diagnosis* was congenital syphilitic aortitis with aortic insufficiency, questionable stenosis or calcification of the aortic ring, and myocardial insufficiency. A roentgenogram of the chest showed enormous enlargement of the left and right ventricles, and pleural effusion at the base of the right lung. An electrocardiogram revealed a high-grade intraventricular conduction defect. Both the blood Wassermann and Kahn reactions were positive (2 plus). The pulse became completely irregular and there was a pulse deficit. Five days after admission, while apparently comfortable, and engaged in conversation, the patient suddenly developed profuse diaphoresis, became markedly cyanotic, and died.

Post-mortem examination revealed syphilitic aortitis and aortic insufficiency; calcific aortic stenosis with an acquired bicuspid condition of the valve; young and old myomalacia of both ventricles; chronic passive congestion of the liver, spleen, kidneys, intestines, and lungs.

The heart was enormous, weighing 1300 gm. The mouth of the right coronary artery was narrowed. The left and right coronary arteries and their branches were sclerotic, but not narrowed. Despite the absence of coronary occlusion, there was an area of softening of recent origin in the anterior wall of the left ventricle near the apex. There were also diffuse areas of myofibrosis throughout both ventricles.

DISCUSSION

The following discussion is limited to a consideration of the occurrence and pathogenesis of certain characteristic symptoms of calcific aortic stenosis, and the diagnosis and differential diagnosis of the disease.

Angina Pectoris.—Angina pectoris has been reported as occurring in 20 to 25 per cent of the cases of calcific aortic stenosis. Cardiac pain, with or without the typical radiation of angina pectoris, and usually due to effort, occurred in nine of our fifteen cases.

The pathogenesis of angina pectoris in this disease has been the subject of considerable discussion but is still obscure. Because of the frequency of a diastolic murmur in association with aortic stenosis, the cardiac pain has been attributed to concomitant aortic insufficiency. Several objections may be raised to this theory. Despite the diastolic murmur, there is no dynamically significant insufficiency; the typical

peripheral circulatory phenomena of free aortic regurgitation are absent unless syphilitic aortic insufficiency is present also. Furthermore, angina pectoris has been observed in cases of calcific aortic stenosis in which there was neither a diastolic murmur nor any other clinical evidence of aortic insufficiency. Three such examples were encountered in our series. Finally, there is some question whether the pain in aortic insufficiency (usually in syphilitic aortic insufficiency) is due to the valvular lesion itself. More probably, the pain results from the narrowing of the coronary ostia which so often occurs in syphilitic aortitis. In cases of rheumatic aortic insufficiency angina pectoris is much more infrequent; it is not typical in that it usually occurs without effort and is associated with vasomotor phenomena. The active myocarditis and the extremely low diastolic pressure frequently found in such cases may account in part for the anginal pain.

More logical theories have attributed the pain in calcific aortic stenosis to myocardial ischemia, but as yet there has been neither anatomic confirmation of the existence of such ischemia nor a clear physiologic explanation for its development. Many observers have been unable to find any narrowing of the coronary arteries, such as might be expected to produce myocardial ischemia. In fact, they have emphasized that these vessels show surprisingly little sclerosis, and that their lumina may even be widened. Boas⁴ found the coronary arteries normal at necropsy in two individuals who had suffered from angina pectoris; in one, death had occurred following an attack which closely resembled acute coronary thrombosis. He concluded that the pain was due to myocardial ischemia caused by an obstruction at the aortic rather than at the coronary orifice, and that associated cardiac failure contributed to the development of the symptoms. This explanation appears obscure since normal aortic pressure is usually maintained even when there is extreme stenosis of the aortic valve. Recently, Contratto and Levine⁷ attributed the angina pectoris to myocardial ischemia caused by suction of blood from the coronary arteries by acceleration of the blood flow past the orifices of these vessels. These authors also quoted the views of Harrison, who suggested that the cardiac pain is due to two factors: (1) the augmented cardiac work, resulting from the elevated intraventricular systolic pressure and from the extremely rapid ejection velocity; and (2) coronary vasoconstriction. The first factor is undoubtedly important, but the second is purely hypothetical.

Our studies offer pathologic and clinical support for the theory that myocardial ischemia is the cause of angina pectoris in calcific aortic stenosis. In some instances we have found severe narrowing of the coronary vessels or their lumina, with or without coronary occlusion and myocardial infarction; in others we have seen acute myocardial damage without recent coronary occlusion. Although in calcific aortic

stenosis the coronary vessels are usually surprisingly smooth, they were significantly narrowed in three of the six nonsyphilitic cases in which angina pectoris was present. In addition, the coronary ostia in these cases were narrowed by calcific plaques in the sinus pockets; in two of the cases there was an old occlusion of a major coronary branch. More significant are the two cases of angina pectoris in which there was evidence of myomalacia of recent origin without coronary occlusion. These cases are important because they are examples of myocardial ischemia, of a degree sufficient to produce acute anatomic alterations, resulting from functional coronary insufficiency. Since these studies, we have observed other instances of aortic stenosis in which there was acute myomalacia without recent coronary occlusion. In view of these evidences of extreme myocardial ischemia due to functional coronary insufficiency, it is reasonable to suppose that similar, though less intense, myocardial ischemia may account for those instances of angina pectoris in which there is no anatomic change either in the heart muscle or in the coronary vessels.

A physiologic explanation of, and support for the existence of, functional coronary insufficiency in cases of aortic stenosis is found in the recent studies of Green.¹⁴ He demonstrated, first, that in cases of aortic stenosis there was a significant reduction in the minute-volume flow through the coronary arteries and, second, that this flow could not easily be increased when there was an enhanced myocardial demand for blood. Despite extreme aortic stenosis, an essentially normal aortic pressure is maintained by the abnormally strong left ventricular contraction that is associated with the tremendous elevation of intraventricular pressure, but, at the same time, the elevated intraventricular pressure diminishes the systolic flow (and minute-volume flow) of blood through the coronaries by compressing the peripheral coronary vessels and thus increasing the coronary resistance during systole. The mechanism is similar to that involved in the blanching of a tightly clenched fist. Thus, there may be an inadequate coronary flow even at rest. Usually, however, this inadequacy becomes significant only during exertion, when an increased coronary flow is needed. Because of the already extremely high intraventricular pressure, the left ventricle finds it difficult, or impossible, to augment further the force of its contraction and the aortic pressure. As a result, there may be, during exertion, an inadequate coronary flow with consequent myocardial ischemia. As long as the heart weight is normal there may be little or no myocardial ischemia, but when the heart is noticeably hypertrophied the ischemia due to a relatively insufficient coronary flow may become intense. This explanation is supported by the fact that, in our series, in those cases in which angina pectoris did not occur the hearts were normal or only slightly hypertrophied, while in those cases in which it did occur the heart weights usually exceeded 500 gm.

The theory that myocardial ischemia is the cause of angina pectoris in cases of calcific aortic stenosis is further supported by the electrocardiographic changes. There is usually left axis deviation, which may, of course, be due to the hypertrophy of the left ventricle. More significant are those changes in the T-wave and RST segments which are frequently encountered in this disease. Because of these changes the electrocardiogram is often interpreted as indicating myocardial disease, and a clinical impression of coronary artery disease is apparently verified. When electrocardiograms are taken repeatedly, the progressive alterations in the T-waves and RST transitions are sometimes interpreted as indicating coronary thrombosis, an interpretation which the clinical picture seems to confirm. These electrocardiographic abnormalities are explicable if we accept the hypothesis that with extreme calcific aortic stenosis there is actually myocardial ischemia similar to that associated with coronary arteriosclerosis or occlusion.

Conduction Disturbances.—Complete heart block, bundle branch block, intraventricular conduction defects, and delayed auriculoventricular conduction occur with sufficient frequency in calcific aortic stenosis to be considered characteristic of the disease.^{4, 15} In the electrocardiograms of the patients in the present series, left bundle branch block was observed three times, intraventricular conduction disturbance (arborization block) twice, and a prolonged PR interval twice. These abnormalities occurred in four of the fifteen cases.

These disturbances in conduction, especially complete heart block, have been attributed to organic disease of the bundle of His, caused by an extension of the calcific process from the aortic valve to the fibrous septum.¹⁵ While we, as well as others,¹⁶ have occasionally observed such calcific destruction of the bundle, we have seen heart block in some cases in which such organic changes could not be demonstrated. Lime salts were not found in the microscopic sections containing the bundle in any of our four cases in which there were conduction disturbances. While this is inconclusive without detailed study of serial sections, there are other reasons for believing that the conduction disturbances are not invariably, nor even usually, due to organic calcific interference with conduction. First, it would be difficult to explain the intraventricular conduction defects, for the calcific process does not extend beyond the main bundle or the beginning of its main branches. Second, the type and degree of conduction disturbance in a given case are often variable and transient. Thus, in one case of calcific aortic stenosis which we have observed (not included in this series), the electrocardiogram first revealed only left axis deviation and a negative T-wave in Lead I. A week later the PR interval was prolonged to 0.28 second. Shortly afterward there was a transient complete heart block and, eventually, an intraventricular conduction disturbance. In Case 4 of Boas²⁴ report, heart

block was likewise transient and occurred only on exertion, simultaneously with angina pectoris. It is difficult to correlate these observations with the conception of a fixed organic calcific lesion in the bundle or its branches. On the other hand, they are clearly compatible with our belief that the disturbances in conduction, like angina pectoris, are due to myocardial ischemia. This does not preclude the fact that in some instances of conduction disturbance calcific deposits in the bundle play a contributory or dominant role.

Dizziness and Syncope.—Gallavardin¹⁷ has stressed the frequency of dizziness and syncope in cases of calcific aortic stenosis. He believes that these symptoms are due to sudden, transient, cerebral anemia, caused by an insufficient aortic output. He bases this belief on electrocardiograms made during syncope of effort, which showed that the heart did not stop contracting while the pulse beat entirely disappeared. Marvin and Sullivan⁶ suggested that syncope, like sudden death in this disease, is due to a hyperactive carotid sinus reflex.

There are two significant observations as to the occurrence of dizziness and syncope which are pertinent to their pathogenesis. In the first place, these symptoms tend to occur in individuals who suffer from angina pectoris and, second, they tend to occur during effort. This suggests a similarity between the mechanism which produces angina pectoris and that which causes dizziness and syncope. Dizziness and syncope, like angina pectoris, occur in those individuals in whom there is extreme narrowing of the aortic orifice, and a consequent marked compensatory hypertrophy of the left ventricle. Under ordinary circumstances the increased intraventricular tension is sufficient to maintain a normal aortic, and consequently a normal cerebral, arterial pressure despite the valvular stenosis. But there is no reserve for further elevation in intraventricular pressure when exertion requires an increase in the cerebral vascular flow. Thus dizziness and syncope result from the cerebral anemia that is caused by a relative cerebral arterial insufficiency.

Sudden Death.—The frequency of sudden death in cases of calcific aortic stenosis has been noted by many authors, but its pathogenesis remains obscure. It occurred in three of our cases. Those individuals who die suddenly of aortic stenosis have usually suffered from angina pectoris, dizziness or syncope, or disturbances in cardiac conduction. The pathogenesis of sudden death would, therefore, seem to be similar to, or identical with, that of the above-mentioned manifestations. The commonest of the natural causes of sudden death is myocardial infarction due to coronary artery occlusion. As we have seen, myocardial infarction may occur in calcific aortic stenosis, due either to associated coronary thrombosis or to extreme coronary insufficiency. In some instances of severe myocardial ischemia death may occur before an infarct has formed. Whether sudden death may also occur in this

disease as a result of myoeardial isehemia insufficient to produce infaretion remains uncertain. Such myoeardial ischemia may, however, be sufficient to produce a high degree of heart block, with consequent eerebral anemia or eardiae standstill, or it may cause ventrieu-lar fibrillation.

Cerebral anemia, as we have seen, may be due directly to an inadequate supply of blood through the eerebral vessels. It may produce merely dizziness or syneope, but oecasionally, if extreme, sudden death. Marvin and Sullivan⁶ have suggested that a hypersensitive earotid sinus also may produce cardiac standstill and sudden death, but Contratto and Levine⁷ were unable to produce dizziness or syneope in nineteen out of twenty-one patients with caleific aortie stenosis by pressing on the earotid sinus. It is possible, however, that when myoeardial ischemia has already produced some degree of conduction disturbance, reflexes from a hypersensitive earotid sinus may help to precipitate sudden death. Two cases have been reported in which sudden death may have resulted from the formation of an occluding thrombus over the stenotic aortie valvular orifice.¹⁸

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

There is no longer any reason why the clinical diagnosis of caleific aortie stenosis should not be made in most instances of the disease. Of course, its recognition is simple when the classical criteria are present, namely, an aortie systolic murmur and thrill, absence of the second aortie sound, a characteristieally small delayed pulse, and enlargement of the left ventriele. Caleific aortie stenosis should be suspected, even in the absenee of a thrill, if there is a very rough, or musical, systolic murmur and enlargement of the heart in a person past 50 years of age with no evidence of organie mitral disease. Calcification of the valves may then be confirmed by roentgenologie examination, especially by fluoroscopy, as described by Sosman and Wosika.⁵

Most frequently the only physical sign of ealcifie aortie stenosis is a loud, rough, whistling or musieal murmur at the base of the heart, over the sternum, or over the entire preeordium. In the absence of hypertension such a murmur should always suggest the possibility of ealcifie aortie stenosis, espeecially if there is evidence of left ventricular enlargement or if there is a history of dizziness, syneope, or angina pectoris, and if there are disturbanees of eardiae eonduction. The provisional diagnosis may then be verified by a roentgenologie demonstration of caleification of the aortie valve.

In about half of the eases of caleifie aortie stenosis there is an assoeiated aortie diastolie murmur suggestive of aortie insuffieieney, but none of the dynamic changes of aortie insuffieieney are present. If an aortie diastolie murmur is heard in a patient who has a negative Was-

sermann reaction, no history of syphilis, no associated mitral lesion, and none of the peripheral circulatory phenomena of aortic insufficiency, a diagnosis of calcific aortic stenosis should be considered and evidence of calcification of the heart valves sought by fluoroscopy.

Calcific aortic stenosis is most often confused with mitral insufficiency, aortic insufficiency, and arteriosclerotic heart disease (coronary artery disease). Mitral insufficiency is considered when, as happens frequently, there is only a systolic murmur. Aortic insufficiency is diagnosed because of the frequent presence of a diastolic murmur at the base of the heart along the sternum. The differentiation of calcific aortic stenosis from these lesions has already been discussed.

The differentiation of calcific aortic stenosis from coronary artery disease may be extremely difficult because, as we have seen, the symptoms of both are due essentially to myocardial ischemia. Angina pectoris, disturbances in conduction, abnormalities of the T-waves, cardiac failure, and sudden death are caused by both of these conditions. Attacks of dizziness and syncope, when present, favor a diagnosis of calcific aortic stenosis, rather than arteriosclerotic heart disease. If, in addition, there is a distinctive murmur or a systolic thrill, the differentiation from coronary artery disease is clear. Calcific aortic stenosis should be considered as a diagnostic possibility in any patient with cardiac failure of obscure etiology. In all doubtful cases the cardiac valves should be examined in detail fluoroscopically and roentgenographically for evidence of calcification.

The differentiation of rheumatic from nonrheumatic calcific aortic stenosis usually cannot be made from the symptoms and physical signs alone. If there is a history of rheumatic fever, a rheumatic etiology is almost certain. If the patient is below the age of 50, the aortic stenosis is usually due to rheumatic fever. When there is definitely an associated mitral stenosis, the aortic, like the mitral, lesion is almost invariably rheumatic. When the physical signs of mitral stenosis are uncertain, roentgenologic evidence of unusual left auricular or right ventricular enlargement suggests associated rheumatic mitral disease. Similarly, if the electrocardiogram shows right ventricular preponderance, due apparently to mitral disease, the calcific aortic stenosis is probably rheumatic.

SUMMARY

1. A study was made of fifteen cases of calcific aortic stenosis in which detailed pathologic examination (previously reported) had shown that the lesion was nonrheumatic. In four of the cases there was an associated syphilitic aortitis.

2. While in most cases of calcific aortic stenosis there is considerable evidence that the etiology of the lesion is rheumatic, this evidence does not preclude the existence of a nonrheumatic form of the disease.

3. The cases in our series fell into three groups. The first, consisting of six cases, was characterized by the development of left- and right-sided heart failure. The history of these patients revealed the typical symptoms of calcific aortic stenosis, including angina pectoris, dizziness, and syncope. Electrocardiograms frequently showed varying degrees of heart block, such as bundle branch block and intraventricular conduction disturbances, and abnormalities of the T-waves and RST transitions. In occasional cases death occurred suddenly.

In the second group, consisting of five cases, the valvular lesion was discovered accidentally in patients who died of some unrelated disease. Neither the characteristic symptoms of the valvular abnormality nor evidences of heart failure were present.

The third group, containing four cases, resembled the first, both in the occurrence of cardiac failure and in the appearance of the other characteristic symptoms. These cases were segregated because there was associated syphilitic aortitis and aortic valvular disease.

4. Seven cases typifying these three groups were presented in moderate detail.

5. The occurrence and pathogenesis of angina pectoris, conduction disturbances, dizziness and syncope, and sudden death were discussed.

A. Angina pectoris is believed to be caused by myocardial ischemia due to coronary insufficiency. When the patient is at rest, coronary insufficiency is due partly to the increased demand for blood made by a greatly hypertrophied heart, and partly to the diminished coronary flow. The coronary flow is reduced by the increased peripheral coronary resistance resulting from the extremely high systolic pressure within the left ventricle. During exertion the coronary insufficiency becomes more marked. Verification of the existence of coronary insufficiency in these cases is furnished by the occasional instances of myocardial infarction without acute coronary occlusion and by the electrocardiograms, which may resemble those of coronary occlusion.

B. The conduction disturbances, as well as the changes in T-waves and RST transitions, were similarly explained as being caused by myocardial ischemia due to coronary insufficiency. Occasionally, heart block is due to extension of the calcific process to the septum, but the nature of some of the conduction disturbances, their occurrence in some patients on effort, and their transience suggested that they were due predominantly to myocardial ischemia.

C. Dizziness and syncope occur almost always on effort. They are thought to be due to cerebral ischemia. The already high left intraventricular pressure necessary to compensate for extreme aortic stenosis can be further elevated only with difficulty when there is a demand for increased cerebral blood flow. Occasionally, a hypersensitive carotid sinus also may play a role.

D. Sudden death in this disease may have various causes. It may be due to coronary thrombosis, or to myocardial infarction resulting from severe ischemia without acute occlusion (i.e., from coronary insufficiency). Occasionally it may be due to severe cerebral ischemia, obstructing thrombi on the stenotic aortic valve, a hypersensitive carotid sinus reflex, cardiac standstill, or ventricular fibrillation.

6. A summary was given of the means of diagnosing calcific aortic stenosis, of differentiating it from the diseases with which it is ordinarily confused, and of distinguishing the rheumatic from the non-rheumatic cases.

REFERENCES

1. Christian, H. A.: Aortic Stenosis With Calcification of the Cusps, *J. A. M. A.* 47: 158, 1931.
2. Margolies, H. M., Ziellessen, F. O., and Barnes, A. R.: Calcareous Aortic Valvular Disease, *AM. HEART J.* 6: 349, 1930-31.
3. McGinn, S., and White, P. D.: Clinical Observations on Aortic Stenosis, *Am. J. M. Sc.* 188: 1, 1934.
4. Boas, E. P.: Angina Pectoris and Heart Block, *Am. J. M. Sc.* 190: 3, 1935.
5. Sosman, M. C., and Wosika, P. H.: Calcification in Aortic and Mitral Valves With a Report of 23 Cases, *Am. J. Roentgenol.* 30: 3, 1933.
6. Marvin, H. M., and Sullivan, A. G.: Clinical Observations Upon Syncope and Sudden Death in Aortic Stenosis, *AM. HEART J.* 10: 705, 1935.
7. Contratto, A. W., and Levine, S. A.: Aortic Stenosis With Special Reference to Angina Pectoris and Syncope, *Ann. Int. Med.* 10: 1636, 1937.
8. Sohval, A. R., and Gross, L.: Calcific Sclerosis of the Aortic Valve, *Arch. Path.* 22: 477, 1936.
9. Mönckeberg, J. G.: Der normale histologische Bau und die Sklerose der Aortenklappen, *Virchows Arch. f. path. Anat.* 176: 472, 1904.
10. Clawson, B. J., Noble, J. F., and Lufkin, N. H.: The Calcified Nodular Deformity of the Aortic Valve, *AM. HEART J.* 15: 58, 1938.
11. Geerling, J. G.: Sclerosis annularis valvularum, Thesis. Univ. Gröningen. Holland, 1929.
12. Giese, W.: Die Verkalkungen des Herzskeletts, *Beitr. z. path. Anat. u. z. allg. Path.* 89: 16, 1932.
13. Gross, L., and Friedberg, C. K.: Lesions of the Cardiac Valves in Rheumatic Fever, *Am. J. Path.* 12: 855, 1936.
14. Green, H. D.: The Coronary Blood Flow in Aortic Stenosis, *Am. J. Physiol.* 115: 94, 1936.
15. Uehlinger, E.: Die Beziehungen der Entzündungen und Sklerosen der Herzklappen zum spezifischen Muskelsystem, *Deutsches Arch. f. klin. Med.* 152: 227, 1926.
16. Yater, W. M.: Pathogenesis of Bundle Branch Block, *Arch. Int. Med.* 62: 1, 1938.
17. Gallavardin, L.: Les syncopes d'effort dans le rétrécissement aortique, *Arch. d. mal. du coeur* 30: 745, 1937.
18. Lutembacher, R.: La mort subite chez les cardiaques, *Presse méd.* 29: 203, 1921.

THE DEVELOPMENT OF THE ELECTROCARDIOGRAM OF THE EMBRYONIC HEART*†

EBBE C. HOFF, PH.D., NEW HAVEN, CONN., T. C. KRAMER, M.A., ANN
ARBOR, MICH., DELAFIELD DuBOIS, A.B., NEW HAVEN, CONN.,
AND B. M. PATTEN, PH.D., ANN ARBOR, MICH.

THE obviously interesting possibilities of electrocardiograms from embryonic hearts have led to many attempts to secure such records. The technical problems involved, however, have proved to be varied and troublesome and the results none too consistent. Physiologists well equipped to deal with the matter of electrical recording have been handicapped by the lack of a detailed knowledge of heart development and by unfamiliarity with satisfactory methods of handling living embryos. Embryologists, to whom a knowledge of cardiac development is a stock in trade, have not been trained to cope with the intricate technique of recording and the difficult matter of interpreting minute electrical changes. With the rapid progress that has been made in electrical recording and in the manipulation of living embryos during recent years, it seemed as if it should be fruitful to attempt a group attack on this problem of the embryonic electrocardiogram, in which the collaborators among themselves would have first-hand knowledge of all the necessary phases of the work.

LITERATURE

As is natural, the earliest work in this field dealt with relatively advanced fetuses which might be expected to furnish records more readily comparable with those from adults. In 1906, Cremer¹ attempted to secure fetal electrocardiograms in the last month of gestation by the use of vaginal-abdominal or recto-abdominal leads on pregnant women. Similar efforts to obtain electrocardiograms from the fetus in utero, using also as variants of Cremer's original method two external abdominal leads, were made by Foà² (1911), Haynal and Kellner³ (1923), Sachs⁴ (1923), and Maekawa and Toyoshima⁵ (1930). The superimposition of a weaker fetal electrocardiogram on a stronger maternal record and the occurrence of irregularities in the records which did not appear to be attributable to either fetal or maternal heart have made the results obtained from such an approach exceedingly difficult to evaluate with any certainty.

*Work aided by a grant from the Fluid Research Fund, Yale University School of Medicine.

†From the Laboratory of Physiology, Yale University School of Medicine, and the Department of Anatomy, University of Michigan Medical School.

Received for publication Oct. 8, 1938.

Greater success has attended efforts to secure electrocardiograms by the use of direct leads from fetuses removed in cases of hysterectomy and kept alive for a time in warm physiologic saline solution. Easby⁶ (1934) has reported on the records of a 4½ month fetus thus obtained, and Heard, Burkley and Schaefer⁷ (1936) succeeded in making good records from a series of eleven fetuses ranging in age from the tenth to the twenty-fifth week of gestation. These observations clearly indicate that the embryo develops an electrocardiogram similar to that of the adult at a surprisingly early age, and that any efforts to study the manner in which the characteristic adult waves are established must be undertaken on embryos in which the early stages of heart formation are occurring. The almost insurmountable difficulty of securing anything like a complete series of living human embryos in this age range has directed attention toward the embryos of animals adaptable to experimental investigation.

Wertheim-Salomonsen⁸ (1913) was the first to study the heart action of really young embryos by electrocardiographic methods. Using the chick as an experimental animal he succeeded in taking records from embryos as young as 60 hours. He was greatly handicapped, however, by the lack of amplification methods such as have since become available, and his records of these early stages showed only slow rises and falls with no clear cut phases such as would be anticipated from what is known of the character of the heart action at this stage. Not until the fifth to sixth day did his records show anything like a regular electrocardiographic pattern beginning to be recognizable. Cluzet and Sarvonat⁹ (1914) and Spadolini and Giorgio¹⁰ (1921) encountered the same difficulties, their records from young embryos showing nothing sufficiently consistent to warrant any attempt at interpretation.

That electrocardiograms of adult pattern are obtainable much earlier than was indicated by such results was shown by Külbs¹¹ (1920), who greatly improved the recording technique and obtained tracings from chick embryos showing the emergence of practically all of the adult characteristics as early as the third day of incubation. In agreement with Külbs' results, Robb,¹² in the abstract of her report to the International Physiological Congress (1929), stated that the beginnings of P-waves and of the QRS-T complex were becoming recognizable between fifty and seventy-two hours.

Further progress in the technique of recording was shown in the work of Lauche and Schmitz¹³ (1931) and that of Lueg and Höfer¹⁴ (1933). Both these papers, however, dealt with explanted hearts or with cultivated heart fragments. Some of such observations, especially those of Lueg and Höfer, and of Katsunuma and Inada¹⁵ (1933), on isolated atrial and ventricular portions of the heart are exceedingly interesting, but they need to be evaluated in relation to records

of the intact heart acting under more nearly normal conditions. Moreover, the hearts studied by these workers were for the most part rather too old to show the most interesting changes involved in the development of an electrocardiogram of adult configuration.

A description of a carefully worked-out technique for recording electrical changes in the embryonic heart was published by Pollack¹⁶ in 1931. This was followed by a paper in collaboration with Dionne and Schafer¹⁷ (1931) on amplification technique, and a later paper by the same group (Dionne, Schafer, and Pollack,¹⁸ 1932) giving some of the results obtained by these methods. The embryos they used were for the most part older than those on which we are reporting, their series running from the fourth to the twentieth day, but when their observations and ours dealt with comparable material it is interesting to note that the potential changes recorded are quantitatively in close agreement. They observed, however, a wave which they called the "P a" wave, with which we found nothing precisely comparable. This wave appeared immediately following the P-wave and was regarded by them as an auricular phenomenon comparable to the T-wave of the ventricular complex. Among our records from older embryos—not here illustrated—puzzling, complex P-waves were occasionally seen. We were inclined to regard them as conduction irregularities caused perhaps by unsuccessful maintenance of favorable conditions in the preparation, rather than as a normal phenomenon. None of them seemed to us to correspond with the "P a" wave described by Dionne, Schafer, and Pollack, unless the rise following the P-wave in Fig. 7 could be so interpreted.

In a short paper on the influence of digitalis on the embryonic electrocardiogram, Lagen and Sampson¹⁹ (1932) state that multiphasic curves are obtainable from chick embryos as early as the thirty-sixth hour of incubation. Regrettably, no illustrations of their records were included, so that satisfactory comparison of their interesting findings with other available data is not possible.

The most satisfactory electrocardiographic records from young embryonic hearts which we have been able to find in the literature are those of Külbs,¹¹ referred to previously, and those of Bogue²⁰ (1933). The records Bogue reproduces are clear-cut and convincing as to the very early appearance of polyphasic tracings. Comparing Bogue's records with those of earlier workers it is apparent that, as amplifying apparatus has improved, the beginnings of the characteristic waves of the adult electrocardiogram have become recognizable in progressively younger embryos. Moreover, it is in these earliest phases of heart development that the most significant changes in the character of its beat are known to occur. For these reasons our own efforts were directed primarily toward securing records from the time the heart beat was just commencing, through the period of rapid

changes in structure and action which occur during loop formation and the establishing of the fundamental regional divisions of the heart.

METHODS

The eggs used were procured locally from white Plymouth Rock hens and artificially incubated by the usual laboratory methods. For taking electrocardiograms, embryos of known incubation ages were removed from the shell to permit concurrent observations of heart action and to facilitate more accurate manipulation. The matter of unhampered manipulation is of particular importance in connection with the precise placing of the microelectrodes, for even slight differences in their position may be of great importance in the interpretation of the records.

The technique of removal and subsequent handling followed in a general way the methods used by Patten and Kramer²¹ (1933) for their microcinematographic recording of the early heart beats. Eggs were opened under saline solution kept at 38° C. By means of a circular cut through the blastoderm, well peripheral to the yolk-sac blood vessels, the embryo was freed from the yolk. After removing the vitelline membrane, the embryo was floated into a shallow Stender dish from which a small quadrant of the side wall had been cut. The excess fluid having been pipetted off, the embryo and its essential membranes were spread out on the bottom of the dish in as nearly as possible their normal position. Small strips of filter paper adherent to the nonvascular periphery of the membranes were used to hold the embryo in position. With the cover in place, such a chamber may be freely handled without injury to the contained embryo. If kept at incubation temperatures, the embryo will live in it for many hours and even continue to grow. There was every evidence, certainly throughout the relatively short period necessary for our observations, that the heart was behaving normally.

The small opening referred to as having been cut in the side wall of the Stender dish served both as means of access for introducing fresh saline solution and for the insertion of the microelectrodes. In another series of experiments, to be reported later, this opening served as a means of introducing drugs. It could readily be covered when not actually in use.

For the taking of the electrocardiographic records the chamber with an embryo mounted in it was placed on the stage of a binocular dissecting microscope in connection with which was mounted a Chambers micromanipulator. The microscope and micromanipulator were housed in a specially constructed, copper-shielded incubator which was suspended by springs from the ceiling of the electrocardiographic room. Working through arm holes in the incubator, it was possible, with the aid of the micromanipulator, to place the electrodes accurately at the desired locations on the embryo. When all adjustments had thus been made the arm holes were closed with copper-shielded doors for the period of the actual recording.

Various types of electrodes were tried, with little indication of differences in their performance. The electrode used in most of the experiments consisted of a small ball of platinum formed at the end of a platinum wire. The wire was enclosed in drawn glass tubing fused around the base of the ball to prevent any liquid from creeping up the wires. A pair of such electrodes, matched as closely as possible, were mounted in adjustable brass tubes which permitted their being firmly clamped in the micromanipulator arms. Immediately before use the platinum balls were coated with platinum black. A second type of electrode which also gave good results consisted of capillary glass tubing containing isotonic saline-agar gel in which chloridized silver wires were embedded.

The changing potentials picked up by the electrodes were first passed through a three-stage amplifier and then recorded with a Hindle electrocardiograph. The first and second stages of this amplifier, together with all the batteries, were housed in a second copper-shielded box suspended below the shielded incubator containing the

It should be emphasized that in using tubes under these unusually exacting conditions each individual tube must be tested, since it is not to be expected that the voltages designated for one will be exactly right even for another tube of the same lot and number. In testing the tubes, characteristic plate current versus grid voltage readings were taken, switching in and out of the grid circuit a resistance of 1.2 by 10^{10} ohms (S. S. White Dental Manufacturing Co.). From the data so obtained two curves can be drawn which cross at "floating grid," when the grid current is zero and when switching in and out of the high resistance has no effect on the plate current. From the divergence of these two curves the magnitude of the grid current at any grid voltage may be calculated. The tubes were studied at various values of heater current, plate voltage, and screen-grid voltage. The 259B tube was operated as follows: Heater current, 1.4 amperes; plate supply voltage, 39; plate voltage, 24; screen-grid voltage, 16.5; grid voltage for floating grid, 0.45. The plate current was 0.15 milliamperes, and the voltage amplification (100,000 ohms plate load) was 24 volts per volt.

The second and third tubes (R.C.A. 38) were used according to the method described by Johnson and Neitzert²³ (1934) except that large, high-resistance condensers were used to adapt the amplifier to heartbeat frequency. The method of balancing off plate current from the galvanometer string is obvious from the diagram. All resistances were wire-wound and soldered in place. Each tube was soldered by the prongs, so that no tube sockets were used, and the electrode, grid, and battery connections were all soldered.

MAJOR CHANGES IN THE STRUCTURE OF THE EMBRYONIC HEART DURING THE PERIOD COVERED BY THE EXPERIMENTS

The embryonic heart, during the early stages of its formation, changes rapidly and radically in structure (Patten,²⁴ 1922). The initial cardiac contractions in a 29- to 30-hour-old chick take place in a heart which has only its ventricular region well formed. The potential changes one records from a chick in which the heart beats are beginning to develop with sufficient power to set the blood in motion are produced by a heart in which both the atrium and the ventricle have begun to beat, but in which the sinus venosus is still too little differentiated to show any contractile activity. Not until some time after the circulation of blood has been well established does the sinus region begin to pulsate and to take over the pace-making role previously carried by the atrium. With such profound changes occurring in the heart it is obviously futile to attempt any interpretation of records of its action except in the light of explicit knowledge of the morphologic changes with which the physiologic changes are correlated.

The most significant thing about the young embryonic heart, which must be understood in order to interpret the functional changes occurring in it, is the fact that its various regional divisions do not start to differentiate simultaneously, but in sequence. The general manner in which the primitive cardiac tube is formed by the coalescence midventrally of paired primordia which first make their appearance on either side of the midline has long been well known. What

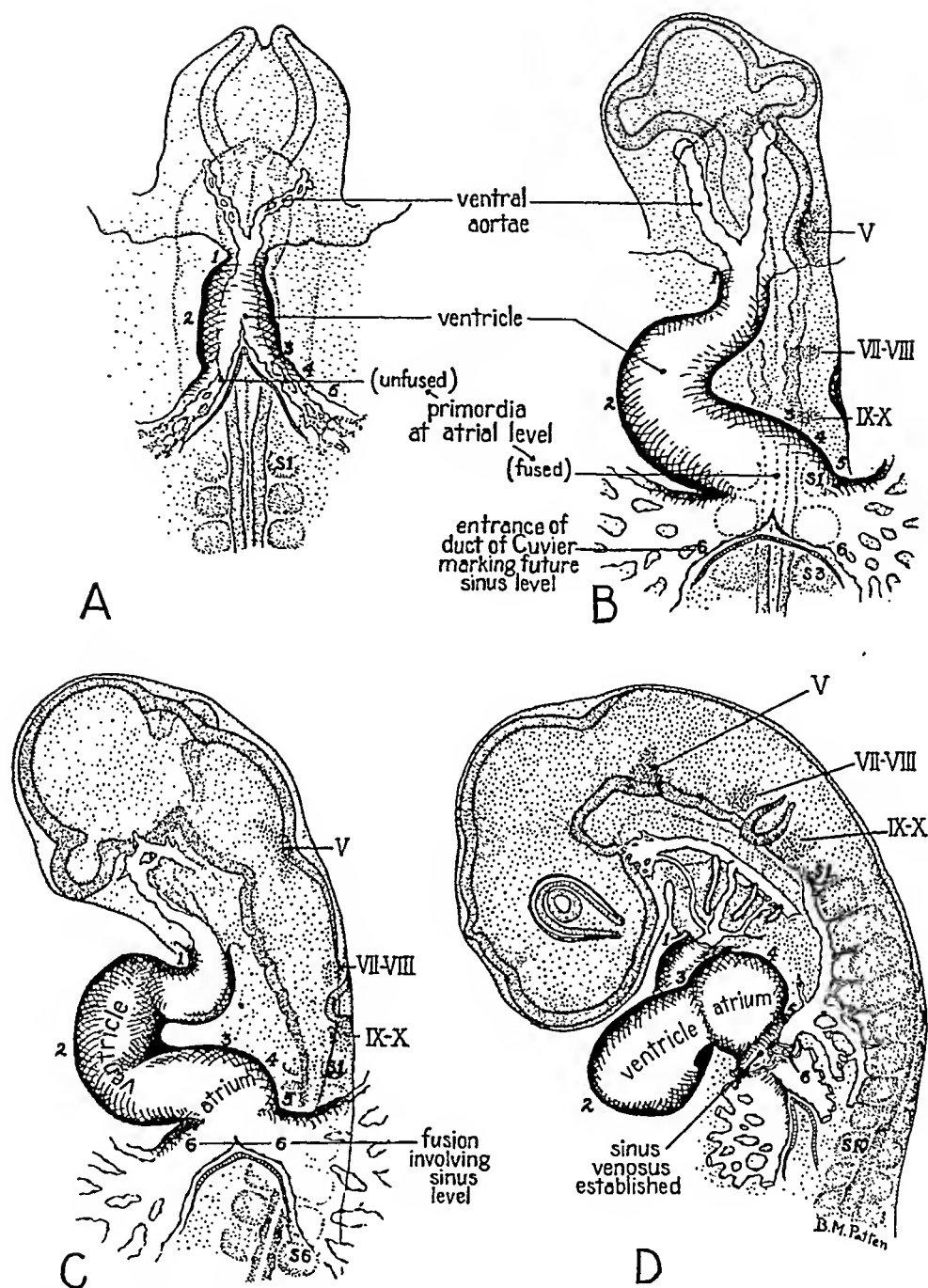


Fig. 2.—The formation of the fundamental regions of the chick heart by progressive fusion of its paired primordia. A, at the 9-somite stage, when the first contractions appear. The bulboventricular part of the heart is the only region where the fusion of the paired primordia has occurred and their myocardial investment has been formed. B, at the 16-somite stage, when the blood first begins to circulate. The atrium and ventricle have been established, but the sinus venosus exists only as undifferentiated primordial channels, still paired and still lacking myocardial investment. C, at the 19-somite stage. Fusion of the paired primordia is just beginning to involve the sinus region. D, at the 26-somite stage. The sinus venosus is definitely established and its investment with myocardium well advanced. While schematic as to manner of drawing, these figures are based on projection outlines of actual preparations, and such structures as the somites and the cranial ganglia V, VII-VIII, and IX-X are shown in their exact relationships to serve as landmarks in following the progress of fusion of the cardiac primordia. As an additional aid in following this fusion, arabic numerals have been placed against approximately corresponding locations. The 6 is located at the point of entrance of the duct of Cuvier as determined from injected specimens. Sabin's³¹ (Legend continued on opposite page.)

has not until recently received sufficient attention is the fact that the fusion of these primordia takes place gradually, being completed anteriorly before it has even begun posteriorly.

The main steps in the sequential formation of the primary regional divisions of the heart are indicated diagrammatically in Fig. 2. Each of the paired cardiac primordia consists of a delicate endothelial tube flanked laterally by a thickened fold of potentially myocardial tissue. As the endocardial tubes meet in the midline they coalesce with each other to form the endothelial lining of the primitive tubular heart. At the same time the myocardial folds of the two primordia meet each other to complete the outer contractile layer of the heart. If we look at an early stage in this process (Fig. 2 *A*) it becomes evident that, with this fusion beginning, as it does, anteriorly, the bulboventricular part of the heart is established before fusion reaches the atrial level at all. The atrium is formed later, behind the ventricle, as fusion of the primordia progresses caudad (Fig. 2 *B*). Still later the sinus venosus is added behind the atrium (Fig. 2, *C* and *D*).

Myocardial differentiation follows this same sequence, and we find the myocardial layer of the ventricle well formed and considerably thickened, while that of the atrium is still undifferentiated. The atrial myocardium in turn differentiates before that of the sinus. The various regions of the heart begin to beat in the same sequence in which they are formed. Feeble local contractions appear first in the ventricular myocardium and, before the atrium has been fully formed, the ventricle has developed a slow but rhythmic beat of its own. When the atrium has been added behind the ventricle and begins to pulsate, we notice that its contractile rate is higher and that it comes to dominate the slower ventricle, thus increasing the heart rate and initiating a peristaltoid sweep of the contractions from posterior to anterior. It is highly significant that this atrioventricular beat becomes adequate to start the actual circulation of blood before the sinus venosus is sufficiently differentiated to show any contractile activity whatever. It is some time after circulation has commenced that the sinus is formed behind the atrium and in its turn invested with myocardial covering. The sinus, when it becomes active, shows an intrinsically higher contraction rate than either ventricle or atrium, and its incorporation into the cardiac tube again increases the heart rate and lengthens and intensifies the peristaltoid sweep of the contractions.

Legend for Fig. 2 (Cont'd)

Figs. 1 and 2, plate 2, show in dorsal perspective the entrance of the duct of Cuvier at stages corresponding to *B* in this figure. The entrance point of the duct of Cuvier serves as a precise indication of the level of future sinus territory. The heavy black outlines and the crosshatched contours indicate the extent to which the heart is invested by differentiated myocardium. Note especially the absence of anything like an effective myocardial layer encasing the sinus region until a considerable time after the heart has begun to beat and the blood has been set in motion.

A fuller account of the changes outlined above will be found in a paper by Patten and Kramer²¹ (1933). The sequential formation of the several regions of the embryonic heart, and the fact that they go into activity in the same order that they are formed is, however, a matter of such fundamental importance for interpreting records of its action that it seemed necessary to summarize this situation briefly here. In comparing records made during this period of rapid changes we must know whether they represent a ventricular beat, an atrio-ventricular beat, or a sinoatrioventricular beat.

RESULTS AND DISCUSSION

The earliest visible manifestation of cardiac activity occurs in chick embryos at the 29- to 30-hour stage (embryos of nine to ten somites). It consists of spasmodic contractions of small groups of cardiac muscle cells which precede the establishment of regular rhythmic contraction of the heart as a whole. These contractions have been recorded microcinematographically (Patten and Kramer,²¹ 1933), and are known to appear first in the primitive ventricular part of the heart. Repeated efforts were made to record the potential changes of these early local contractions but we obtained no satisfactory tracings. This was particularly disappointing in view of the interesting comparison they would have afforded with the potential changes reported by Hogg, Goss, and Cole²⁵ (1934) for small clusters of cultured ventricular muscle cells from the embryonic heart of the rat.

Our earliest consistent records were from embryos in the 33- to 36-hour range (thirteen to fifteen somites). At this stage of development, fusion of the cardiac primordia has progressed caudad so that it is just beginning to involve the atrial level (Fig. 2 *B*). The heart beat is regular, although still slow in rate, and is beginning to show a peristaltoid character with the beat starting near the atrioventricular junction and sweeping cephalad through the ventricle. Fig. 3 shows the progression of the contraction as recorded by micromoving pictures. An electrocardiographic record taken at this stage is reproduced in Fig. 4.

In the usual electrocardiographic setup, relative negativity of the right-hand electrode produces an upward movement in the tracing. In making our records from the embryonic heart the apparatus was so arranged that the more cephalically placed electrode corresponded to the conventional right-hand electrode. With these facts as to the experimental conditions in mind, and with a timed record of the progress of contraction such as that shown in Fig. 3 for comparison, the general significance of the electrical record seems clear. The initial drop in the tracing indicates the initiation of contraction nearer to the posterior electrode, so that the anterior (right-hand) electrode is first positive. As the impulse moves forward through the ventricle,

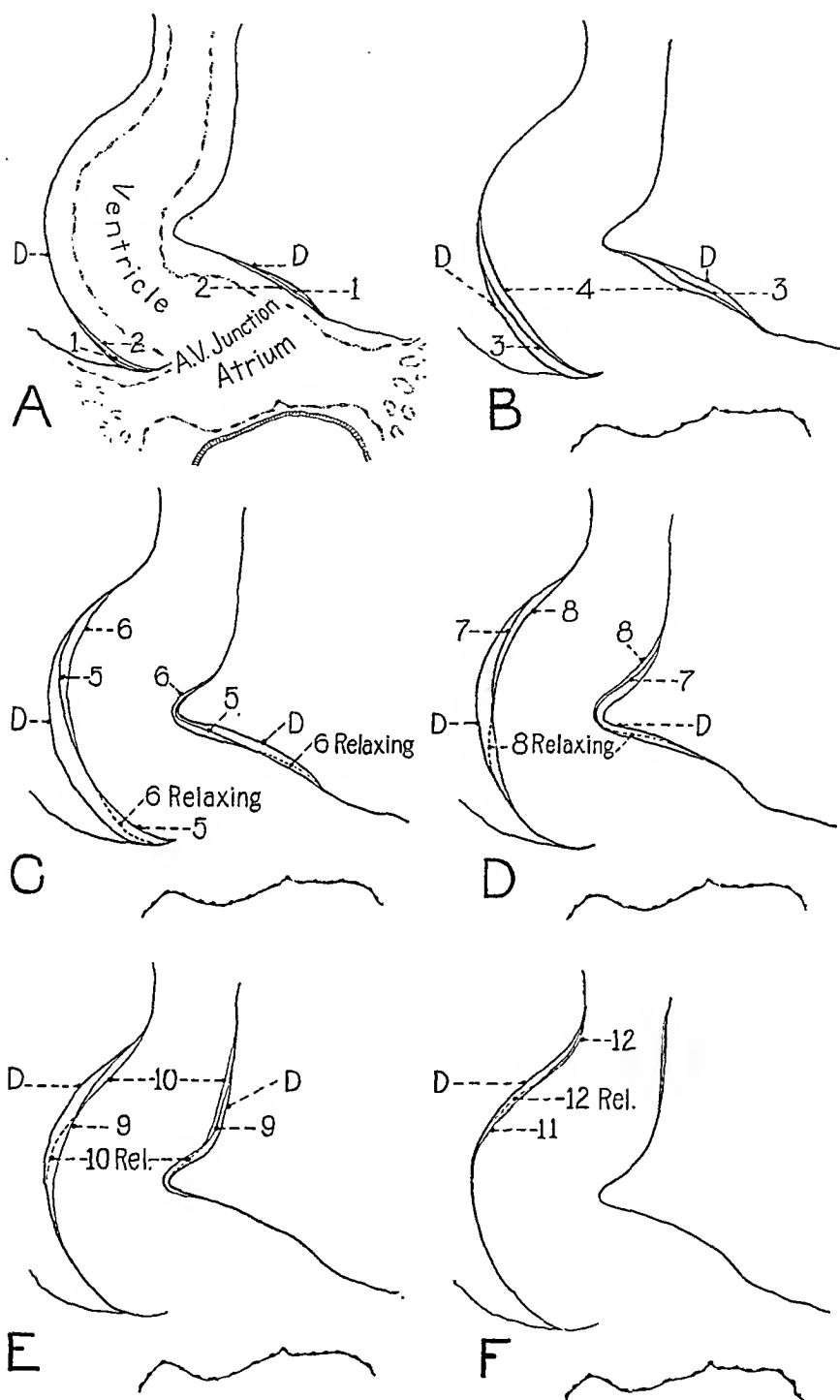


Fig. 3.—Superimposed tracings from micromoving pictures (sixteen frames per second) of heart at stage when the atrium is being established behind the ventricle (12 to 13 somites; \pm 32 to 33 hours' incubation). The outer solid line is the tracing of the heart contour during diastole. The numbered contour lines are tracings from successive frames, indicating the contraction changes at one-sixteenth-second intervals during one complete contraction cycle. Where beginning relaxation has brought a contour line nearer to the diastolic outline than the previous frame, the line is drawn broken.

the anterior electrode becomes relatively negative and the tracing sweeps above the isoelectric line. That the initial deflection is downward rather than upward clearly reflects the fact that in the very young embryonic heart the cephalocaudal position of ventricle and atrium is exactly the reverse of that characteristic of the adult, the atrium in the young embryo being more posterior than the ventricle.

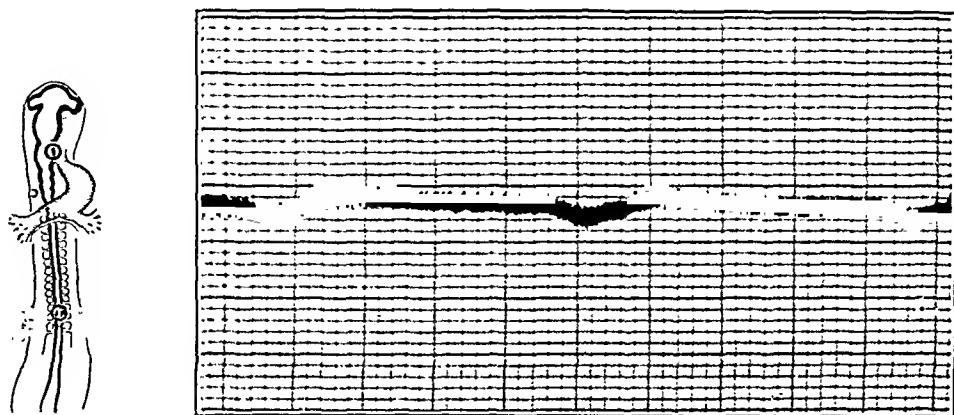


Fig. 4.—Tracing from a 15-somite chick (No. 79, "incubation age" \pm 36 hours). Platinized platinum electrodes. Calibration: 50 microvolts = 12 mm.

In this and the following figures the diagram at the left showing the shape and position of the heart was made by projection from a photomicrograph of the actual embryo yielding the record. The small circles indicate the positions in which the electrodes were applied.

The sinusoidal configuration of such tracings from very young hearts calls for additional comment. Almost all the earlier workers in this field have secured tracings of a similar character from "the youngest stages successfully recorded." But repeatedly, as methods have improved, the sinusoidal type of curve has been reported as characteristic of younger and younger embryos, and clear-cut polyphasic tracings have been obtained from embryos of ages at which earlier investigators secured only sinusoidal curves. Eyster, Krasno, and Hettwer²⁶ (1937) attribute this situation to the fact that with unsatisfactory amplification methods the string had to be unduly loosened to respond at all to the minute potential changes involved. They are inclined to believe that the heretofore reported sinusoidal curves had no significance other than indicating the use of too loose a string. In the light of what has happened in the past, the possibility must be frankly faced that further refinements in technique may result in supplanting with more definite records the sinusoidal curves we obtained from our youngest stages. It is pertinent, nevertheless, to emphasize the fact that our amplification was sufficient to permit taking the record reproduced in Fig. 4 with the string at the normal tightness used for the entire series of observations here reported. Perhaps worthy of comment, also, is the fact that this earliest electrical record of ventricular contraction in the embryonic heart is

strikingly similar to records taken from dying human hearts in the terminal stages of ventricular fibrillation.

Electrocardiograms from slightly older embryos begin to show a sharp downward deflection (Fig. 5) instead of the sinusoidal curve of the earliest records (Fig. 4). We interpret this deflection as being

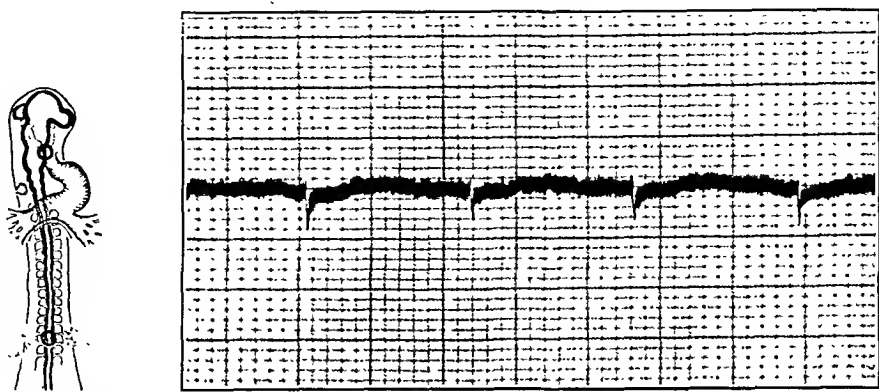


Fig. 5.—Tracing from 16-somite chick (No. 71, "incubation age" \pm 38 hours). Platinized platinum electrodes. Calibration: 50 microvolts = 10 mm.

the first manifestation of the QRS or characteristic ventricular complex. There are several points to be considered in arriving at such a conclusion. In the first place, it must be remembered that the heart at this stage is still almost entirely ventricle, and that the atrial region is just beginning to be formed behind the ventricle as fusion of the paired cardiac primordia progresses caudally. Other points of significance can be gleaned from microscopic observation of the character of the heart beats, and from experiments in which the heart is transected at various levels.

When compared with earlier stages, the heart at the stage when this deflection first begins to appear in the electrical records can be seen to have increased its rate, and it will be noted that the individual beats start off decidedly more abruptly. Morphologically, the heart, during this period, has grown in length as fusion of the paired primordia progresses. As the more posterior parts of the cardiac primordia are added to the growing cardiac tube they seem to be bringing in muscular tissue with a higher intrinsic contraction rate than that possessed by the muscle in the more anterior parts of the heart previously formed. This is suggested both by the rate increase which occurs as the heart elongates, and by the fact that the beat becomes more definitely peristaltoid in character with its incipience unmistakably in the posterior part of the heart. The differences in intrinsic contraction rate can be clearly demonstrated by transection experiments. Cuts made in the region which is destined to be the atrioventricular junction seem to yield the sharpest differences in

rate, but regional boundaries are as yet only vaguely suggested and it should not be inferred that there is necessarily any precise level at which there is an abrupt change in inherent contraction rate. Whatever future work may show as to the exact location, and the abruptness of transition in rate, that a gradient in inherent contraction rate exists is beyond doubt. It has been repeatedly demonstrated by cutting experiments (Fano and Badano,²⁷ 1890; Lewis,²⁸ 1924; Patten and Kramer,²¹ 1933; Paff,²⁹ 1935) and by physiologic separation of different areas of the cardiac tube by compression (Pickering,³⁰ 1893; Johnstone,³¹ 1924). In the light of such experiments we must conclude that one of the most significant things happening at this stage of heart development is the incorporation into the posterior end of the growing cardiac tube of progressively more tissue with a higher intrinsic contraction rate. As one might expect, the region with the highest contraction rate sets the pace for the heart as a whole. This can be demonstrated, as was done by Paff²⁹ (1935), by growing the severed parts of a heart in close proximity to each other in culture media and watching the more rapidly beating posterior fragment assume control of the slower beating anterior fragment when a bridge of tissue grows across the cut and places the two pieces again in physiologic continuity. Such an experiment complements beautifully those already discussed in which we have seen the ventricle, when severed from the more posterior part of the heart, revert to the slow nonperistaltoid beat which was characteristic for that region when it was the only part of the heart which had been differentiated and had become active.

Applied to the interpretation of the electrical records reproduced in Figs. 4 and 5, these considerations have led us to conclude that both are records of beats which are still essentially ventricular, although at slightly different developmental phases. The appearance of the sharp downward deflection in the record from the older embryo which was absent in that of the younger we would attribute to the incorporation into the cardiac tube of enough new tissue of higher intrinsic contraction rate to increase the pace of the heart as a whole and to start the contractions off "with a sharp kick." With regional boundaries as vague as they are in such young hearts, it would be unwise to attempt to make any too dogmatic statements as to just how this tissue of higher rhythmicity is disposed with reference to the boundaries which will later be established between atrium and ventricle. The two regions are still at this stage directly continuous, and what little of the future atrial region is formed may well be acting physiologically with the ventricle. In any case there is at this stage so little of the sinoatrial portion of the heart formed and active that one can scarcely regard the action currents obtained as anything else than essentially ventricular.

The next significant change in the character of the records appeared in chicks of about 42 to 44 hours of incubation (twenty somites). At this stage of development fusion of the paired cardiac primordia has progressed caudad to such an extent that the atrial region of the heart is well established and the sinus venosus is just beginning to take shape (Fig. 2 *C*). Records at this stage (Fig. 6) show a small downward deflection coming about two twenty-fifths of a second ahead of the QRS waves. This we believe to be the first appearance of the P-wave. The fact that it is at this stage inverted seems in accord with the fact that the sinoatrial region is still the most posterior part of the heart, so that the impulse is passing toward, rather than away from, the cephalic (right-hand) electrode.

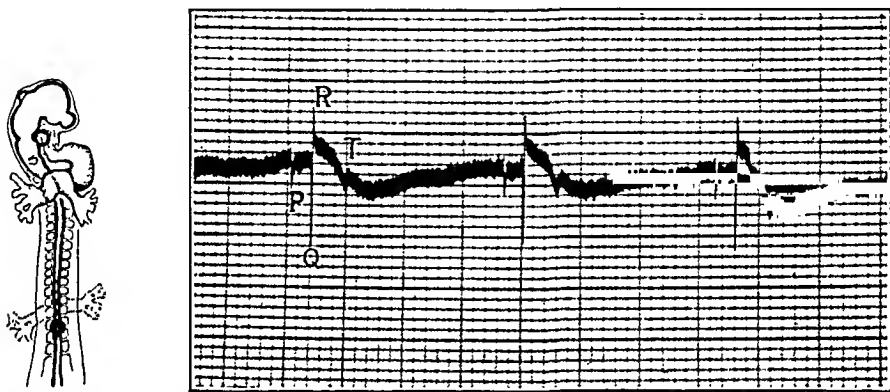


Fig. 6.—Tracing from 20-somite chick (No. 86, "incubation age" \pm 42 hours). Capillary glass electrodes, chloridized silver wire embedded in saline-agar gel. Calibration: 50 microvolts = 10 mm.

Between 44 and 60 hours of incubation the configuration of the chick heart is changing exceedingly rapidly. The sinus venosus is definitely formed during this period and the ventricular loop is carried backward into its definitive position posterior to the atrium (Fig. 2, *C* and *D*). During the early part of this period the P-wave is likely to start with a downward throw just as it did when it made its first appearance, but it may end with an excursion above the isoelectric line (Fig. 7). A little later it may be almost unrecognizable (Fig. 8), and still later be entirely an upward throw as it is in the adult (Fig. 9). It seems probable that this apparently erratic behavior of the P-wave can be explained, at least in part, on the basis of the positional changes which are occurring in the heart. At the beginning of this period the beat is starting in the posterior atrial region where the sinus venosus is just beginning to take shape. This is, at this time, the most posterior part of the heart, and an impulse starting there must pass forward into the atrium and thus might be expected to produce an initial downward deflection in the records. The fact that the ventricular end of the atrium at this stage is bent more or less

backward, along with the ventricle, might possibly be the reason for the terminal upward deflection seen in the P-wave of Fig. 7.

The flattening out of the P-wave in Fig. 8 might be accounted for by the fact that with the heart in this stage of loop formation the sinus is becoming more dorsally located while the ventricle projects ventrally. An impulse starting in the sinus and going toward the ventricle would be passing more or less at right angles to a line connecting the electrodes and so produce little departure from the isoelectric line. Following similar reasoning, when the ventricle has come to lie definitely caudal to the sinoatrial part of the heart, the progress of the impulse would be away from the cephalic (right-hand) electrode and the P-wave should appear above the isoelectric line in its characteristic adult form, as was the case in the record reproduced in Fig. 9. It is quite possible, also, that the somewhat more dorsal position of the cephalic electrode used in taking the record of Fig. 9, as compared with that shown in Fig. 8, may have helped to bring out a positive P-wave.

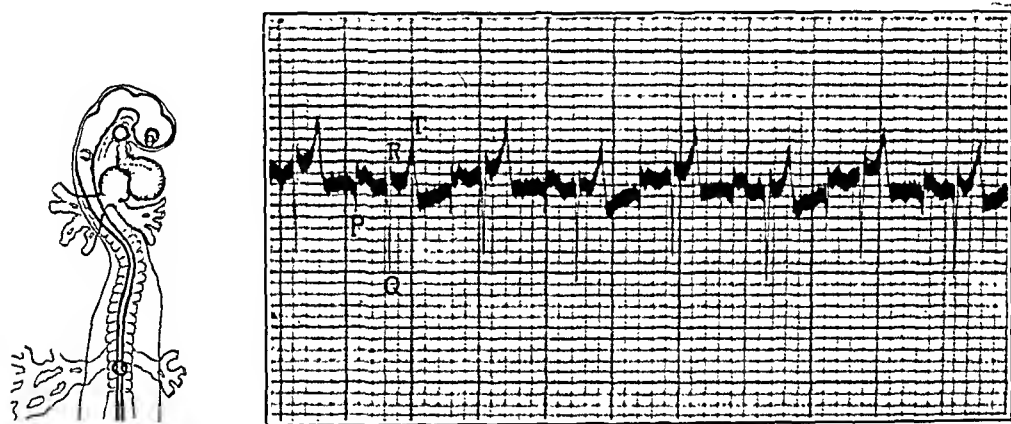


Fig. 7.—Tracing from 24-somite chick (No. 90, "incubation age" \pm 48 hours). Capillary glass electrodes, chloridized silver wire embedded in saline-agar gel. Calibration: 50 microvolts = 15 mm.

The rather startling upward deflection shown following the QRS complex in Fig. 9 is puzzling. It appeared quite conspicuously in most of the records taken in this general age range, but was not usually as strongly marked as in this record from chick number 69. Other than the quite obvious fact that it looks like an exaggerated T-wave, we have no suggestion as to its interpretation.

During the fourth day of incubation the electrocardiogram settles into a pattern which is remarkably like that of the adult (Fig. 10). At this stage of development no nerve connections have been made with the heart. In a careful study of serial sections, the nearest to the heart that any migrating neuroblasts were found was in the loose mesenchymal tissue around the dorsal aortic roots. This tends to confirm the opinion of His³² (1891) that it is certainly not before the end of the fifth or the beginning of the sixth day that the innervation of

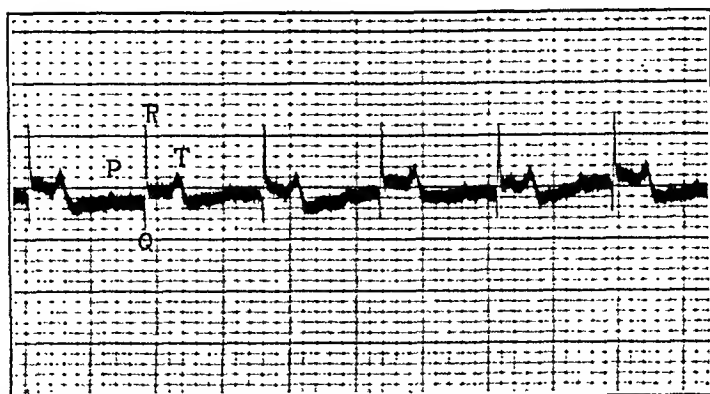
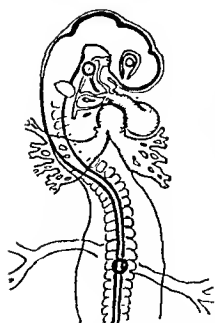


Fig. 8.—Tracing from 31-somite chick (No. 68, "incubation age" \pm 61 hours). Platinized platinum electrodes. Calibration: 50 microvolts = 12 mm.

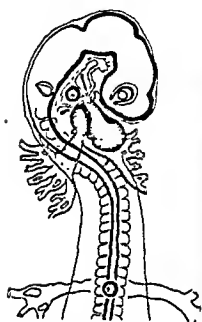


Fig. 9.—Tracing from 29-somite chick (No. 69, "incubation age" \pm 58 hours). Platinized platinum electrodes. Calibration: 50 microvolts = 12 mm. Although this embryo had fewer somites than No. 68, its heart is definitely further advanced in the process of loop formation. Such variability in the relative rates at which embryonic structures differentiate is quite common and frequently necessitates, as in this case, an arbitrary sequencing on the basis of the rate of progress in the organ under special consideration.

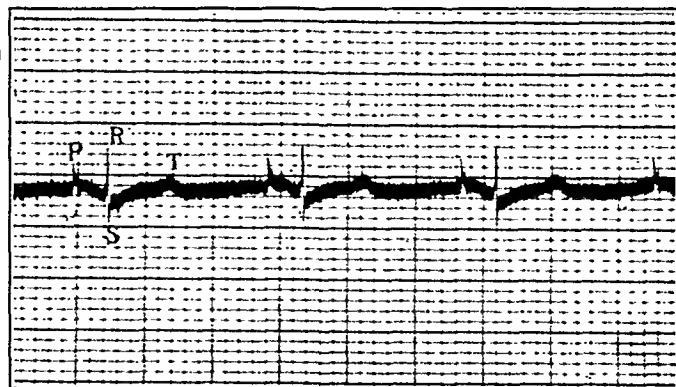


Fig. 10.—Tracing from four-day chick embryo (No. 66). Platinized platinum electrodes. Calibration: 50 microvolts = 11 mm.

the heart is established. Throughout the period covered by the records here presented, therefore, the question of nervous control cannot be raised.

It is of interest, also, that even in the four-day chick heart, which shows a definite atrioventricular sulcus, there has been no separation of atrial and ventricular musculature by ingrowth of connective tissue. It is this secondary ingrowth of connective tissue which, by separating (except for a narrowed bridge in the position of the main His bundle) the hitherto continuous muscle of atrium and ventricle, first makes the sinoventricular conduction system identifiable (His,³³ 1933). It should be emphasized, moreover, that such an identification on the basis of topography can be made a considerable time before it is possible to differentiate the conduction bundle histologically from the rest of the cardiac muscle. In these experiments, therefore, we have been dealing with hearts in which no nerve connections have been established, and the conduction system as we know it in the later stages of the embryo and in the adult has not yet taken shape.

SUMMARY

With the aid of three-stage amplification, electrocardiographic records were made from chick embryos during the early stages of heart development. The youngest embryo from which records were obtained successfully was a fifteen-somite chick. At this stage, which is reached on the average with about 33 to 36 hours of incubation, the nearly straight tubular heart consists almost entirely of ventricle. The electrical record obtained from it shows none of the deflections characteristic of the adult electrocardiogram, but takes the form of a curve which first drops below, and then rises above, the isoelectric line. This configuration is consistent with the posteroanterior direction of the progress of contraction shown by superimposed tracings of successive frames from micromoving pictures of the heart action at this stage.

Slightly older embryos (sixteen to seventeen somites, average incubation age 37 to 40 hours) yield a record in which there appears a sharp downward deflection, followed by a rapid return to, or above, the isoelectric line. Because of its characteristic configuration and because morphologic studies indicate that the embryonic heart at this stage is practically all ventricle, we interpret this as representing the QRS complex.

In the next three or four hours of development, fusion of the cardiac primordia progresses caudally, so that the atrial region becomes definitely differentiated and the sinus venosus begins to take shape posterior to the atrium. Records from embryos in this age range show the appearance of a downward deflection coming about two twenty-fifths of a second ahead of the QRS complex. This we interpret as an inverted P-wave.

During the next day of development the ventricular loop is bent backward so that it comes to be in its adult position caudal to the sinoatrial part of the heart. With this shift in relative positions the P-wave appears above the isoelectric line. Thus by the fourth day of development the electrocardiogram has assumed practically its adult configuration.

It is to be emphasized that not even wandering neuroblasts reach the heart until considerably later in development than the age range covered in these experiments. Furthermore, "conduction tissue" is not at these ages histologically distinguishable from the remainder of the cardiac muscle. Thus we can trace the appearance of all the major features of the adult electrocardiographic pattern in embryonic hearts so young that they completely lack either a nerve supply or a specialized sinoventricular conduction system.

REFERENCES

1. Cremer, Max: Ueber die direkte Ableitung der Aktionsströme des menschlichen Herzens vom Oesophagus und über das Elektrokardiogramm des Fötus, *München med. Wehnschr.* 53: 811, 1906.
2. Foà, Carlo: L'electrocardiogramme foetal, *Arch. ital. de biol.* 56: 145, 1911.
3. Haynal, E., und Kellner, D.: Elektrokardiogrammstudien am Foetus in Utero, *Ztschr. f. klin. Med.* 98: 365, 1923.
4. Sachs, H.: Elektrokardiogrammstudien am Foetus in Utero, *Pflüger's Arch. f. d. ges. Physiol.* 197: 536, 1923.
5. Maekawa, M., and Toyoshima, J.: Fetal Electro-Cardiogram of the Human Subject, *Acta scholae med. univ. imp. Kioto* 12: 519, 1930.
6. Easby, Mary H.: Electrocardiograms From a Four and a Half Months Old Fetus, *AM. HEART J.* 10: 118, 1934.
7. Heard, J. D., Burkley, G. G., and Schaefer, C. R.: Electrocardiograms Derived From Eleven Fetuses Through the Medium of Direct Leads, *AM. HEART J.* 11: 41, 1936.
8. Wertheim-Salomonsen, J. K. A.: Das Elektrokardiogramm von Hühnerembryonen, *Pflüger's Arch. f. d. ges. Physiol.* 153: 553, 1913.
9. Cluzet and Sarvonat: L'electro-cardiogramme de l'embryon de poulet, *J. de physiol. et de path. gén.* 16: 802, 1914.
10. Spadolini, I., and Giorgio, A.: L'elettrocardiogramma Embrionale, *Arch. de fisiol.* 19: 479, 1921.
11. Külbs, F.: Experimentelle Untersuchungen am Hühnerembryo, *Cremer's Beitr. z. Physiol.* 1: 439, 1920.
12. Robb, Jane S.: The Elemental Character of Embryonic Electrocardiograms, *Am. J. Physiol.* 90: 496, 1929.
13. Lauche, A., and Schmitz, W.: Versuche zur Elektrokardiographie pulsirender Gewebeskulturen von embryonalen Hühnerherzen, *Naturwissenschaften* 19: 1042, 1931.
14. Lueg, W., and Höfer, K.: Elektrokardiogramme von embryonalen Hühnerherzen in der Gewebeskulturen bei gleichzeitiger Kinematographien des Bewegungsablaufs, *Deutsch. med. Wehnschr.* 59: 452, 1933.
15. Katsumuma, S., and Inada, G.: Über Elektrokardiogramme von simultaner Herzmuskelkontraktion in einem Gewebekultur Medium, *Nagoya J. M. Sc.* 7: 53, 1933.
16. Pollack, H.: Electrocardiographic Studies on Chick Embryo Hearts. I. A Technic for Recording Electrical Changes in Isolated Chick Embryo Hearts, *J. Lab. and Clin. Med.* 16: 1194, 1931.
17. Pollack, H., Dionne, M., and Schafer, E.: Electrocardiographic Studies on Chick Embryo Hearts. II. An Amplifying Device for Use With a String Galvanometer, *J. Lab. and Clin. Med.* 16: 1198, 1931.
18. Dionne, M., Schafer, E., and Pollack, H.: Developmental Aspects of the Electrocardiogram, *Proc. Soc. Exper. Biol. & Med.* 29: 82, 1931-32.

19. Lagen, J. B., and Sampson, J. J.: Influence of Digitalis on the Electrocardiograms of the Chick Embryo, *Proc. Soc. Exper. Biol. & Med.* 29: 735, 1932.
20. Bogue, J. Y.: The Electrocardiogram of the Developing Chick, *J. Exper. Biol.* 10: 286, 1933.
21. Patten, B. M., and Kramer, T. C.: The Initiation of Contraction in the Embryonic Chick Heart, *Am. J. Anat.* 53: 349, 1933.
22. Pearson, G. L.: Fluctuation Noise in Vacuum Tubes, *Bell System Technical Journal* 13: 634, 1934.
23. Johnson, E. A., and Neitzert, C.: The Measurement of Small A. C. Voltages at Audiofrequency, *Rev. Scient. Instruments* 5: 196, 1934.
24. Patten, Bradley M.: The Formation of the Cardiac Loop in the Chick, *Am. J. Anat.* 30: 373, 1922.
25. Hogg, B. M., Goss, C. M., and Cole, K. S.: Potential in Embryo Rat Heart Muscle Cultures, *Proc. Soc. Exper. Biol. & Med.* 32: 304, 1934.
26. Eyster, J. A. E., Krasno, M. R., and Hettwer, J. P.: Electrical Potentials of the Heart of the Chick Embryo, *Am. J. Physiol.* 120: 173, 1937.
27. Fano, G., and Badano, F.: Étude physiologique des premiers stades de développement du coeur embryonnaire du poulet, *Arch. ital. biol.* 13: 387, 1890.
28. Lewis, W. H.: The Influence of Temperature on the Rhythm of the Isolated Heart of the Young Chick Embryo, *Johns Hopkins Hosp. Bull.* 35: 252, 1924.
29. Paff, G. H.: Conclusive Evidence for Sino-Atrial Dominance in Isolated 48-Hour Embryonic Chick Hearts Cultivated in Vitro, *Anat. Rec.* 63: 203, 1935.
30. Pickering, J. W.: Observations on the Physiology of the Embryonic Heart, *J. Physiol.* 14: 383, 1893.
31. Johnstone, P. N.: Studies on the Physiological Anatomy of the Embryonic Heart. I. The Demonstration of Complete Heart Block in Chick Embryos During the Second, Third and Fourth Days of Incubation, *Johns Hopkins Hosp. Bull.* 35: 87, 1924.
32. His, W. Jun: Die Entwicklung des Herznervensystems bei Wirbelthieren. *Abhandl. d. math-phys. Klasse d. Kgl. Sächs. Gesellsch. d. Wiss.* 18: S. 1, 1891.
33. His, W. Jun: Zur Geschichte des Atrioventrikulärbündels, nebst Bemerkungen über die embryonale Herztätigkeit, *Klin. Wehnschr.* 12: 569, 1933.
34. Sabin, F. R.: Origin and Development of the Primitive Vessels of the Chick and Pig, *Carnegie Contributions to Embryology* 6: 61, 1917.

Department of Clinical Reports

TETRALOGY OF FALLOT: CORRELATION OF CLINICAL, ROENTGENOLOGIC, AND POST-MORTEM FINDINGS

JOSEPH A. PESCATORE, M.D., JOSEPH B. WOLFFE, M.D.,

AND VICTOR A. DIGILIO, M.D.

PHILADELPHIA, PA.

A TRUE case of tetralogy, as described by Fallot,¹ includes the following: (1) stenosis of the pulmonary artery, (2) enlarged and hypertrophied right ventricle, (3) displaced aorta, and (4) interventricular septal defect. The following case is a typical illustration of the tetralogy of Fallot and offered an opportunity to study the relationship of the chambers and great vessels to one another and to the chest wall.

J. B., a man 20 years old, died of septic endocarditis complicating the tetralogy of Fallot. This patient had been under the care of one of us (J. B. W.) for many years. In the summer of 1933 he developed a septic endocarditis, which was the cause of his death in September of the same year.

A roentgenogram taken three years before death (Fig. 1) reveals the typical cardiac silhouette usually seen in these cases, with blunting of the apex and a roughly rectangular heart.

We were interested in ascertaining what anatomic structures were responsible in our case for the typical cardiac silhouette, and therefore an autopsy was performed in the following manner: On opening the chest by removing the sternum and ribs, the size, shape, and position of the heart and its anatomic relation to the lungs were carefully studied. These organs, together with the liver, were removed *in toto*, and were arranged on the x-ray table in exactly the same anatomic relationship which they had occupied in the body. A cannula was inserted into the superior vena cava and tied to prevent leakage. A large metal syringe filled with barium emulsion was then connected to this cannula and the barium slowly injected until the right auricle was completely filled (seen fluoroscopically). A roentgenogram (Fig. 2) showed complete filling of the right auricle, with some of the barium going through the tricuspid opening. The valve and trabeculae carneae are also visualized. This roentgenogram definitely shows that the right auricle forms the right border of the heart and a goodly portion of its anterior surface. In addition, the inferior vena cava, with its contributing branches, is seen coming from the liver and emptying into the right auricle.

The injection of barium was continued and another roentgenogram taken (Fig. 3). It reveals partial filling of the right ventricle, with some of the barium going into the aorta; as expected, marked narrowing of the pulmonary artery is very evident.

Again we continued the injection of barium until we completely filled the right ventricle (Fig. 4). Here we can see that the anterior surface of the heart is formed almost completely by the right auricle and right ventricle, while only a very small portion of the left ventricle can be seen. The apex is blunted and is formed com-

From the Department of Medicine, Temple University Hospital.

Received for publication Sept. 5, 1938.

pletely by the right ventricle, instead of the left, as in normal hearts. Again the marked stenosis of the pulmonary artery is very evident and the aorta contains more barium. After roentgenograms of the right heart were taken, the organ was washed out as well as possible and a hypodermic needle substituted for the cannula (superior vena cava) as a landmark. The cannula was then inserted into one of the pulmonary veins and another roentgenogram taken (Fig. 5). The barium-filled syringe was connected to the cannula and the material slowly injected until the left auricle was

Fig. 1.

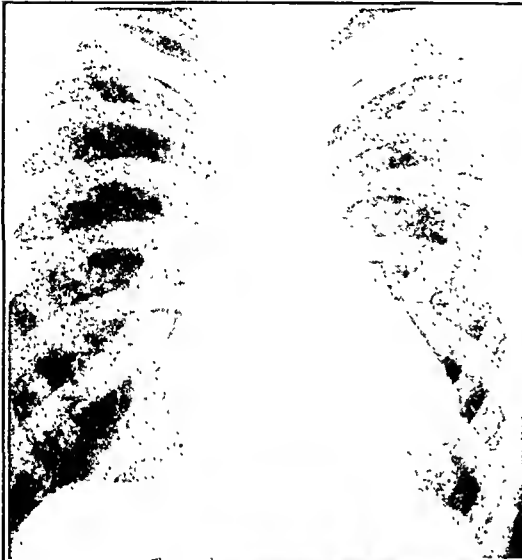


Fig. 2.

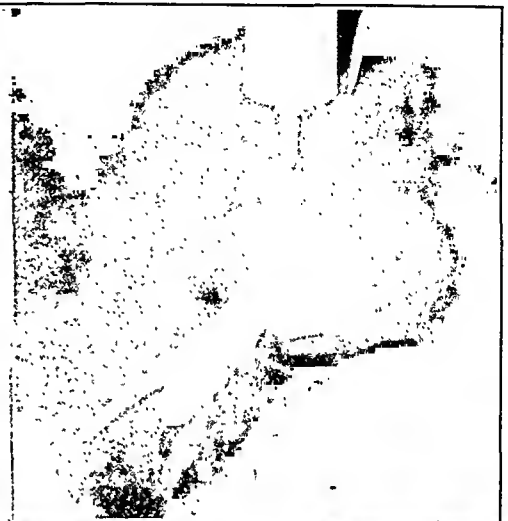


Fig. 3.

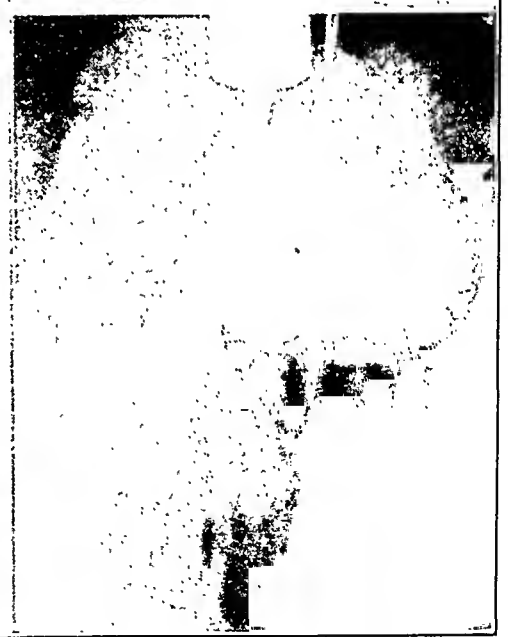


Fig. 4.

filled (Fig. 6). This roentgenogram shows the filled-out left auricle with some of the material going through the mitral opening into the left ventricle, and some going through to the aorta. The pulmonary and hepatic arterial trees are also shown. If Fig. 2 be superimposed upon Fig. 6, it will be seen that the left auricle occupies a position posterior and somewhat medial to the right auricle. The injection of barium was then continued until the left ventricle was completely filled (Fig. 7). This roentgenogram shows that the left ventricle lies almost entirely behind and is

small as compared to the right ventricle. It is also very interesting to note that, although there exists an opening in the membranous portion of the interventricular septum, the barium fails to go into the right ventricle. It may be possible that nature prevents the blood from going from the left to the right ventricle by developing the moderator band, which may act as a valve in closing off the septal opening

Fig. 5.

Fig. 6.



Fig. 7.

Fig. 8.

during cardiac systole. The barium was then forced in under great pressure and Fig. 8 taken. This shows that under pressure the barium finally went through the interventricular opening into the right ventricle, and then into the pulmonary artery. Next, the heart was dissected and washed and a window cut into the right ventricle (Fig. 9). This shows the enlarged right ventricle with its hypertrophied

Fig. 9.

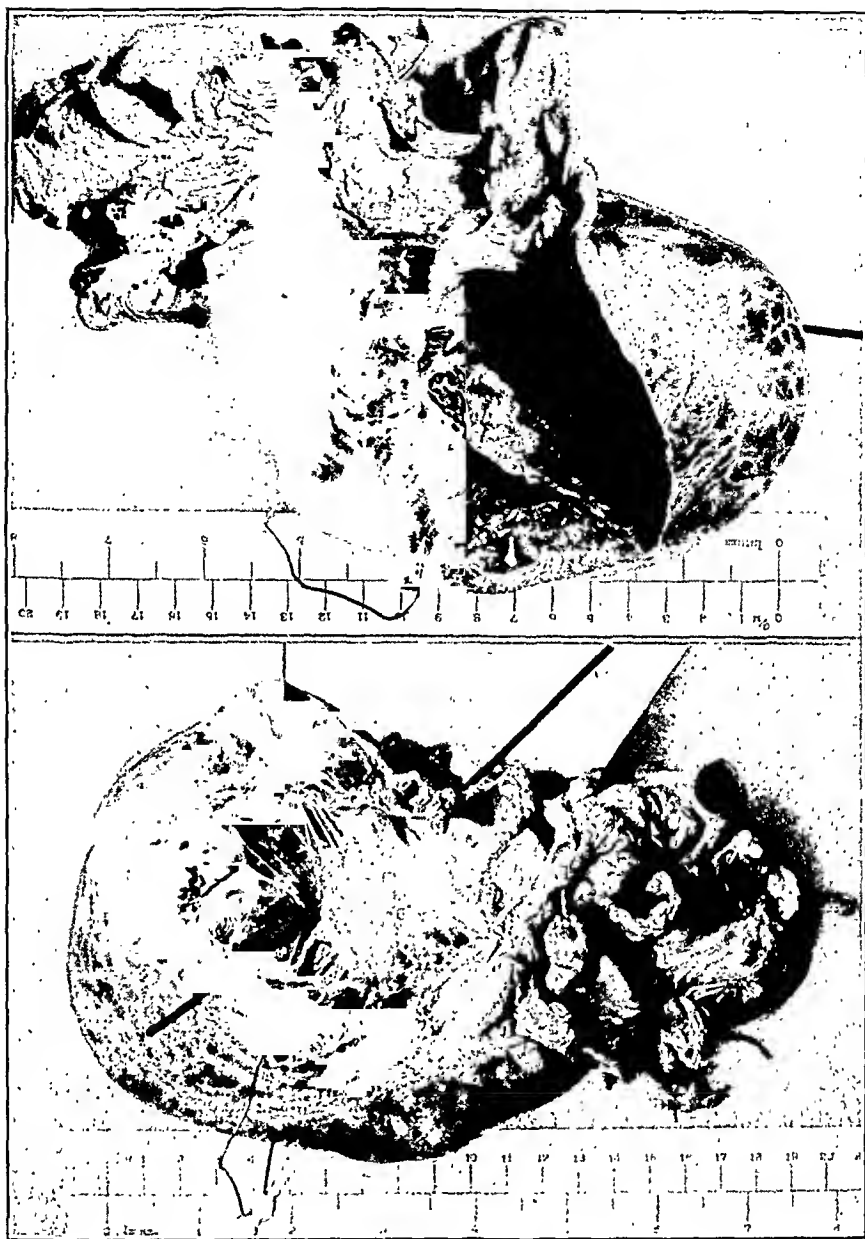


Fig. 10.

walls and, in addition, the interventricular opening with the displaced aorta and stenosed pulmonary artery. A window was then cut into the left ventricle (Fig. 10), showing the small size of this chamber as compared to a normal one; a probe which is running through the interventricular opening is also seen. Finally, a drawing of the anterior aspect of the heart was made in such a way that the picture was a trifle smaller than the original. This was then superimposed on a roentgenogram taken ante mortem (Fig. 11), in order to show the reason for the typical silhouette and the position of the various chambers.

COMMENT

From a diagnostic point of view, Blackford² stresses the rectangular appearance of the heart and its increased transverse diameter. He also



Fig. 11.

points out that the apex of the heart is formed entirely by the right ventricle, instead of by the left, as is the case in the normal heart. These observations deserve emphasis as an aid in the diagnosis of this condition. We attach significance to the blunted appearance of the apex roentgenographically.

Popp³ establishes the following criteria for the roentgenologic diagnosis of tetralogy of Fallot: (1) Absence of the pulmonic conus as a sign of hypoplasia of the pulmonary artery; (2) deviation of the vascular pedicle to the right—*aorta du cheval*; (3) masking of the aorta by the trachea in the right anterior oblique position, and (4) crossing of the aorta by the right bronchus.

Abbott,⁴ largely on the basis of the studies by Sir Arthur Keith, ascribes the lesions of the tetralogy of Fallot to an arrest of development of the cardiac apparatus before the eighth week of embryonic life.

CONCLUSION

We have presented a case of tetralogy of Fallot, and have endeavored to show which anatomic structures are responsible for the typical cardiac silhouette.

REFERENCES

1. Fallot: Original monograph (1888).
2. Blackford, L. M.: Tetralogy of Fallot: Report of a Case, Arch. Int. Med. 45: 631, 1930.
3. Popp, C.: Radiologic Diagnosis of Tetralogy of Fallot, Arch. d. mal. du coeur 24: 249, 1931.
4. Abbott, M. E.: Congenital Cardiac Disease (in Osler and McCrae): Modern Medicine, Ed. 3, Vol. 4, p. 613, Philadelphia, 1927, Lea & Febiger.

MERCURIAL DIURETICS IN CARDIAC FAILURE

REPORT OF A CASE IN WHICH THREE HUNDRED FORTY-THREE INJECTIONS WERE GIVEN*

M. H. FINEBERG, M.D.
CLEVELAND, OHIO

BECAUSE there is still some fear in the minds of practitioners regarding the possibility that repeated injections of mercurial diuretics may have deleterious effects, I am reporting the following case of a patient who received 343 injections of salyrgan and mercupurin over a period of seven and a half years without evidence of any harmful effect.

Dixon¹ reported a case in which 150 injections were given; Maxwell, Scott, and Harvey² reported one in which 198 were given; Levine³ reported one in which 250 were given; and Wiseman⁴ reported another in which 270 were given.

REPORT OF CASE

L. R., a white man 48 years old, was admitted to Mt. Sinai Hospital Sept. 2, 1930, as a private patient of Dr. Harry J. Kumin, and then transferred to the Medical Service of Dr. Samuel S. Berger. On admission the patient presented the typical clinical and electrocardiographic findings of acute coronary occlusion. In February, 1931, he was admitted to the Cardiac Clinic with signs of congestive failure, and he continued to have more or less cardiac failure from this time until his death on April 20, 1938. During this period the patient was admitted to the hospital eight times for increasing degrees of failure; several of the exacerbations were thought to be due to fresh coronary occlusions.

During the period from October, 1930, to April, 1938, this patient received a total of 343 injections of salyrgan and mercupurin in doses varying from 2 to 4 c.c. The injections were given intravenously until obliteration of all accessible veins forced us to use the intramuscular route. The response to these mercurial diuretics remained good throughout, and attempts to discontinue their use were attended with such an increase of the edema and visceral congestion that the patient would literally beg for the injections (unpleasant as they were after they had to be given intramuscularly).

In addition to the above, the patient was kept on a maintenance dose of digitalis, and the action of the mercurial diuretics was augmented at different times by the administration of ammonium chloride, ammonium nitrate, potassium chloride, and aminophyllin.

The urine contained small amounts of albumin throughout, with casts occasionally. On Nov. 19, 1936, the nonprotein nitrogen of the blood was 38 mg. per 100 c.c., and the creatinine 1.6 mg. per 100 c.c. Unfortunately, the obliteration of the patient's veins by the frequent mercurial injections made it impossible to obtain further samples of blood for chemical examination. However, examination

*From the Medical Service and Cardiac Clinic of Mt. Sinai Hospital of Cleveland.
Received for publication Oct. 2, 1938.

of the urine a short time before death (March 21, 1938) showed only a trace of albumin and a few leucocytes.

The patient died suddenly at home, and permission for an autopsy could not be obtained.

SUMMARY

A case is reported of a patient who received 343 injections of salyrgan and mercupurin over a period of seven and a half years without any deleterious effect.

REFERENCES

1. Dixon, I. M.: Salyrgan: Its Long-Continued Use in Cardiac Insufficiency with Latent Edema, *New England J. Med.* 210: 800, 1934.
2. Maxwell, E. S., Scott, J. W., and Harvey, J.: A Study of the Effect of Mercurial Diuretics on Kidney Disease, *J. A. M. A.* 101: 2074, 1933.
3. Levine, S. A.: *Clinical Heart Disease*, p. 299, Philadelphia, 1936, W. B. Saunders Company.
4. Wiseman, J. R.: The Prolonged Use of Salyrgan as a Diuretic: Report of Two Hundred and Seventy Injections in Five Years in One Case, *J. A. M. A.* 99: 114, 1932.

FATAL HEMORRHAGE FROM A PERSISTENT RIGHT DORSAL AORTA TERMINATING IN THE LOWER LOBE OF THE RIGHT LUNG

WILLIAM E. GOODPASTOR, M.D.*
PITTSBURGH, PA.

ANOMALOUS branches of the descending aorta arising in the immediate proximity of the diaphragm are apparently rare. In a search of the literature no report of an aortic branch similar to that described below was found.

The case considered is that of a child who died of pulmonary hemorrhage from an anomalous branch of the aorta. The artery arose from the abdominal aorta immediately below the diaphragm and terminated in the inferior portion of the lower lobe of the right lung.

REPORT OF CASE

The essential history is that of repeated pulmonary hemorrhages occurring in a 10-year-old male negro over a period of two years. For this reason the child was admitted to the Children's Hospital of Pittsburgh on Oct. 20, 1937, and again on Nov. 18, 1937. The hemorrhages recurred at intervals of from two weeks to two months. Occasionally they occurred during sleep, and at other times appeared to have been precipitated by excitement or physical exertion. The amount of blood lost each time varied from approximately 200 to 400 c.c. There were no significant abnormal physical findings other than those indicating consolidation of the lower lobe of the right lung and secondary anemia. The roentgenogram showed a large area of consolidation below the hilum of the right lung. A severe secondary anemia was present. On the first admission examination of the blood gave the following results: hemoglobin 34 per cent; red blood cells 1,950,000; white blood cells 8,600; neutrophils 82 per cent; lymphocytes 18 per cent; reticulocytes 0.9 per cent. A moderate amount of anisocytosis and poikilocytosis was present. Frequent transfusions diminished the degree of the anemia. The temperature remained at about 99° F. The pulse rate varied between 90 and 105; this tachycardia was probably due to the secondary anemia.

The history, physical findings, roentgenogram, negative tuberculin test, negative blood Kahn reaction, and anemia suggested as possible primary diagnoses lung abscess, bronchiectasis, or a growth obstructing a bronchus.

Death finally resulted from a massive hemorrhage. Autopsy showed that death was caused by rupture of an anomalous branch of the aorta within the lower lobe of the right lung, followed by aspiration of blood into the alveoli.

Autopsy Findings.—The only significant pathologic changes found at autopsy were confined to the chest. The pericardial sac was somewhat dilated and contained 150 c.c. (estimated) of clear straw-colored fluid. The heart was somewhat dilated with respect to all its chambers. It measured 11 by 7 by 5 cm. and weighed 207 gm. The cut surface of the cardiac muscle was of a dusky-red hue. The mitral orifice measured 7.5 cm. in circumference, the tricuspid 9 cm. Both easily admitted the index finger. The aortic ring measured 5.5 cm., the pulmonary 6 cm., in circum-

*From the Pathological Laboratories, University of Pittsburgh, and Children's Hospital.

Received for publication Oct. 3, 1938.

ference. The valves contained the normal number of leaflets, and there was no evidence of vegetations or of any sclerosis. The common carotid and subclavian arteries seemed slightly larger than normal. The ductus arteriosus and foramen ovale were closed. Upon dissecting out the descending aorta, a large branch, measuring 1.0 cm. in diameter, was found arising from the right side, just posterior and inferior to the diaphragm. This branch coursed almost vertically upward to enter the diaphragmatic surface of the lower lobe of the right lung near its posterior margin. Within the lower posterior portion of this lobe there was a firm mass about 4 cm.



Fig. 1.—Photograph showing heart and anomalous artery leaving the descending aorta and entering the inferior surface of lower right lung lobe. The relative position of the lung has been disturbed in order to show the manner of entrance of the anomalous artery. Note the vessel does not enter at the hilum.

in diameter which was dark red in color. The anomalous vessel described above entered the inferior surface of this mass. Upon longitudinal section of this vessel it was found that it terminated within the middle of the mass as a network of rather large-calibered vessels, which apparently ended blindly. The lumina of these vessels were filled, in many instances, with organized clot. The vessels lay in close relationship with the bronchioles. No direct communication between vessel and bronchiole was found, although such a communication must have existed. The apex of the left lung was attached to the parietal pleura by fibrous adhesions. Throughout the left lung and the upper and middle lobes of the right lung there were scattered hemorrhagic areas, measuring about 1 cm. in diameter, which were fairly uniformly distributed. The cut surface showed that the alveoli were filled with blood. Microscopic examination showed that the main pathologic changes were in the lungs. In some areas the alveoli were filled with blood; in others there was compensatory emphysema. In

the blood-filled alveoli there were numerous large macrophages which contained blood pigment and particles of carbon. A few similar macrophages were found in the bronchioles. The alveolar walls of the air-containing sections were thickened because of the presence of congested capillaries, small round cells, and a few neutrophils. The anomalous artery showed some early atheromatous changes in the deeper layers of the intima.

DISCUSSION

Two possibilities as to the developmental origin of this vessel have been considered. The first is that this anomaly may have arisen from the distal portion of a persistent right dorsal aorta. The second possibility is that this anomaly may have originated from the persistence of both the right dorsal aorta and one of several of its branches. These branches include the dorsal part of the sixth (pulmonary) arch and a series of branches of the right dorsal aorta which arise caudad to the sixth arch and enter a capillary network in the developing lung.

Orientation with respect to the anlage of the anomaly may be obtained by a brief review of some features of the development of the aortic arch system. Early in development there exists an arterial trunk, or sac, located ventrally in the embryo. From this trunk there proceed two vessels which arch dorsally and then extend caudad. These two vessels are the right and left dorsal aortas (Fig. 2). The left dorsal aorta forms the greater part of the descending aorta of the adult. The right and left fuse for some distance at their caudal extremities (Fig. 2). The unfused portion of the right aorta, distal to the final origin of the right subclavian artery, normally becomes obliterated^{1, 2} (Fig. 2).

This anomaly may be ascribed to failure of the above-mentioned obliteration of the right aorta to occur. Normally the caudal portions of the two dorsal aortas fuse as a result of an initial connection by transverse capillary anastomoses between the two vessels.² The highest cranial level at which the two paired aortas fuse and then proceed as one vessel is known as the region of bifurcation¹ (Fig. 2). It is at this level that the vessel in the case here reported should have arisen. In attempting to place the ultimate level of the region of the bifurcation of the aorta in the human embryo, Congdon² says: "It is probable that a rather common type of anomalous subclavian described in the adult indicates roughly by its origin the ultimate position of the region corresponding to the former bifurcation." These anomalous subclavians are associated with a failure of the caudal part of the paired right aortas to become obliterated.^{1, 2, 3} In this respect their origin is similar to the vessel under discussion. According to Congdon² "(Abnormal) subclavians of this kind are found in the adult arising from the termination of the arch or the aorta as far caudad as the fifth thoracic vertebra. Since the subclavian and other branches of

the arch shift cranially upon it (the aorta), there is a possibility that the aortic wall derived from the earlier region of the bifurcation lies still lower."

It is unfortunate that at the time of autopsy we did not accurately determine the vertebral level of the origin of the anomalous vessel. Roughly, however, it arose at the level of the second or third lumbar vertebra. This level, then, is in harmony with Congdon's concept that at some time the level of the bifurcation of the aorta lies lower than the fifth thoracic.

It seems probable that the network of vessels within the lung tissue had its origin in the postbranchial pulmonary plexus (Fig. 3) which had maintained connection with the persistent right dorsal aorta by one of its several branches. These branches include the dorsal root of the right sixth arch (Figs. 2 and 3) and a series of six additional branches which in the embryo are found arising from the dorsal aorta caudad to the sixth arch (Fig. 3).

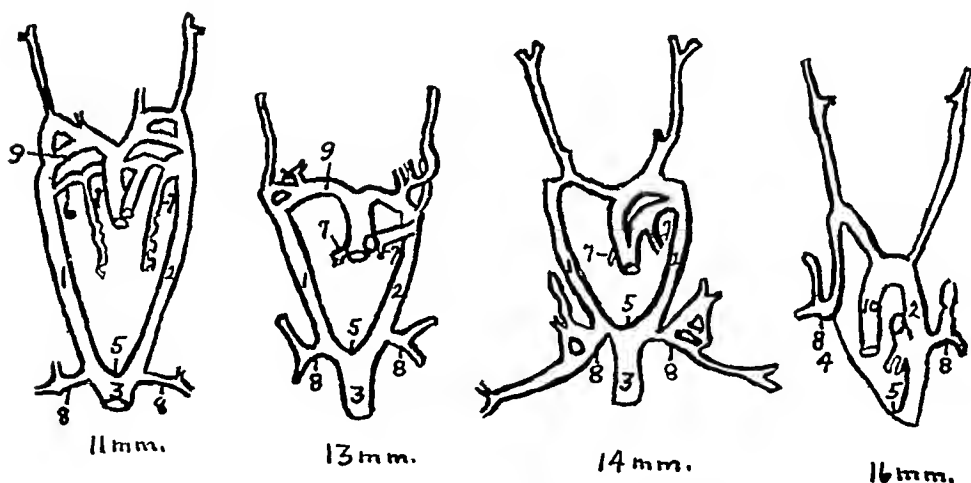


Fig. 2.—From Congdon, E. D.: Contributions to Embryology, Carnegie Institute of Washington Publication No. 14, 47, 1922 (slightly modified). Ventral views of aortic arch system, showing successive developmental stages in human embryo: 1, right dorsal aorta; 2, left dorsal aorta, the descending aorta in the 16 mm. embryo; 3, fused portion of right and left dorsal aortas; 4, the obliterated right dorsal aorta, the probable origin of the anomalous vessel here discussed; 5, region of bifurcation of the aorta placed at the level of the second or third lumbar vertebra in the case here considered; 6, dorsal root of the sixth arch which becomes obliterated in process of normal development; 7, pulmonary arteries; 8, subclavian arteries; 9, fourth right arch; 10, ascending aorta.

The embryology of the sixth arch and the aortic branches which enter the pulmonary plexus may be summarized briefly as follows: In the embryo the ventral arterial trunk and the two dorsal aortas are connected by a series of paired arches. Each arch, with the exception of the transient fifth, contributes in part to the adult arterial system. It is with the sixth that the discussion here is concerned. The sixth arch is tapped on either side by a branch from the pulmonary plexus of vessels.^{4, 5} These branches develop into the pulmonary

arteries. The part of the left sixth arch distal to the origin of the branch forms the ductus arteriosus, later the ligamentum arteriosus. The corresponding distal part of the right sixth arch becomes obliterated entirely in normal development (Fig. 2). Failure of this portion to become obliterated and a persistence of its connection with the right dorsal aorta is therefore ventured as one explanation for the peculiar pulmonary termination found in this case.



Fig. 3.—From Huntington, G. S.: *The Anatomical Record* 17: 165, 1919-20 (slightly modified). Right side of 4 mm. cat embryo: A, aorta; 1 to 6, aortic arches; 7 to 10, branches of the thoracic aorta entering postbranchial pulmonary plexus; L, pulmonary anlage.

With regard to the sixth arch and the other vessels which connect the aorta and pulmonary plexus in the embryo, Huntington⁵ has the following to say: "The dorsal rudiment of the sixth arch arises from the dorsal aorta, extending cranial as a short spur. This I shall designate as the cranial member in a series of aortic derivatives which, inosculating in a capillary network, form what may be defined as the postbranchial pulmonary plexus (Fig. 3), in view of the part it takes in the development of the pulmonary artery ----- . The succeeding two components (7, 8) follow in close proximity to 6, ----- . The ninth aortic derivative enters the plexus considerably further caudad ----- ." Further dorsal aortic tributaries in the cat embryos described by Huntington numbered as many as twelve. Of older embryos Huntington⁵ says: "The plexus as a whole is in the process of abandoning its primary multiple aortic connections and of transferring to the new line of the future pulmonary artery, initiated by its junction with the caudal spur from the ventral segment of the sixth arch." A persistence of one of these branches of the right dorsal aorta may offer a satisfactory explanation for the pulmonary termination of the persistent right dorsal aorta.

SUMMARY

A case of an anomalous branch of the descending aorta arising below and close to the diaphragm has been described. Its probable origin as a persistence of a part of the right dorsal aorta or of this vessel together with one of its early pulmonary branches has been discussed.

I wish to thank Dr. Maud L. Menten, Pathologist to the Children's Hospital of Pittsburgh, for the privilege of presenting this case and for the guidance which has made this discussion possible. Dr. Maude E. Abbott, in a personal communication with Dr. Menten, has confirmed the concept that this anomalous vessel arose from the right dorsal aorta.

REFERENCES

1. Sprague, H. D., Ernbind, C. H., and Albright, F.: Clinical Aspects of Persistent Right Aortic Root, *New England M. J.* 209: 679, 1933.
2. Congdon, E. D.: Transformation of the Aortic-Arch System During the Development of a Human Embryo: Contributions to Embryology, Carnegie Institute of Washington Publication No. 227, 14, 47, 1922.
3. Arkin, A.: Totale Persistenz des rechten Aortenbogens im Röntgenbild, *Wien. Arch. f. inn. Med.* 12: 385, 1926.
4. Buell, C. E., Jr.: Origin of the Pulmonary Vessels in the Chick: Contributions to Embryology, Carnegie Institute of Washington Publication No. 227, 14, 11, 1922.
5. Huntington, G. S.: The Morphology of the Pulmonary Artery in the Mammalia: *The Anatomical Record* 17: 165, 1919-20.

CONGENITAL ATRESIA OF THE AORTIC VALVE WITHOUT SEPTAL DEFECT

REPORT OF CASE

STUART LIPPINCOTT, M.D., C.M.*

MONTREAL, CANADA

MANY slight developmental anomalies of the heart, such as a persistent foramen ovale or ductus arteriosus, are not associated with a definite clinical picture and are therefore of no particular practical interest. In these cases the cardiovascular changes which normally take place shortly before or after birth are delayed for a variable period. They represent, therefore, simply transient arrests in development. In contrast to this group, the following unusual case is reported because it combines a number of true errors and defects in development of the heart and its great vessel attachments. The outstanding feature was complete atresia of the aortic valve with hypoplasia of the ascending aorta. Only seven such cases have been collected in a review of the recent literature. An analysis of a total of 4,364 post-mortem examinations performed at the McGill Pathological Institute from 1919 to 1933 disclosed thirty-five cases of congenital heart anomalies (Table I). In this series there were only two instances of complete aortic atresia, one of which is herewith recorded.

Analysis of Thirty-Five Autopsy Cases of Congenital Heart Disease

1. Defects of Interauricular Septum	
Patent foramen ovale	2
2. Defects of Interventricular Septum	
At base without dextroposition	6
Defects elsewhere, or multiple	5
3. Complete Defects of Cardiac Septa	
Cor triloculare biatriatum	2
Cor biloculare	1
4. Transposition of Arterial Trunks	
Complete transposition	
Closed interventricular septum	2
Defect interventricular septum	1
5. Pulmonary Atresia	
With closed interventricular septum	1
6. Aortic Stenosis and Atresia	
Aortic stenosis	4
Aortic atresia	1
7. Anomalies of Semilunar Cusps	
Bicuspid aortic valve	2
Defect of aortic valve	1
8. Tricuspid and Mitral Stenosis	
Mitral atresia	2
9. Anomalies of Auriculoventricular Cusps	
Defect tricuspid valve	1
10. Hypoplasia of Aorta	3
11. Anomalies of Great Veins	
Pulmonary	1
Total	35

*From the Pathological Institute of McGill University, Montreal. Prof. Horst Oertel, Director.

Received for publication Oct. 5, 1933.

A satisfactory classification of congenital heart disease is difficult. This is not only because a great variety of anomalies may occur, but also because some are complicated by intrauterine infections. A classification based on a correlation of the clinical and anatomic facts has been outlined by Abbott,¹ and this has been applied to the findings in this case.

REPORT OF CASE

Clinical Note.—The clinical course was very brief. The baby was delivered spontaneously; it was a breech presentation. The mother was a well, active woman, giving no history of infection. For the first three days following birth the baby was apparently normal, and then suddenly refused to nurse. He died seventy-six hours after he was born. There was at no time any cyanosis or dyspnea. The physical examination revealed no murmur, thrill, or any other evidence of cardiac defect. The liver was palpable, but not the spleen. A lumbar puncture was performed and blood was found in the cerebrospinal fluid, but this blood was thought to have been introduced by the puncture. Adrenal hemorrhage was suspected as the cause of death.

Abbreviated Protocol.—Case 17626, Autopsy No. 162-34. (The autopsy was performed forty-two hours post mortem.) The body was that of a large, well-nourished baby, 51 cm. long and weighing 3,640 gm. There was no edema. Post-mortem lividity was diffuse. The thorax was symmetrical and the abdomen rounded. The center of ossification was present in the lower end of both femurs.

On opening the thorax, the transverse diameter of the precordium measured 6 cm. and that of the pericardium 7.5 cm. The thymus was large, pinkish-red, lobulated, and contained scattered petechiae. The trachea contained a small amount of curd. The lungs were of usual size, shape, and consistency. They were smooth, glistening, crepitant, elastic, and pinkish-red, both on pleural and cut surfaces. The bronchi were free, with light red mucosa. These represent normal findings for this age. The heart is subsequently described in detail.

On opening the abdomen, the subcutaneous fat was 1 cm. thick. The liver was 4 cm. below the costal angle, 5 cm. below the right costal, and 2 cm. below the left costal margin, in the midclavicular line. The diaphragm extended to the fourth intercostal space on both sides. The spleen weighed 20 gm.; its capsule was smooth and glistening and it was dark red. The cut surface showed gray, prominent, lymph follicles surrounding the dark red hemorrhagic pulp. The kidneys weighed 20 gm. each and were similar. The capsule stripped readily, revealing a red, smooth surface with fetal lobulations. The cut surface showed a pale red cortex with darker medulla, each in normal relation. The bladder was empty; its mucosa was smooth and white. The testes were normal. The stomach and large and small intestines had an intact, pale gray mucosa. The pancreas showed no anatomic lesion, and the adrenals were markedly autolyzed. The liver weighed 170 gm.; its capsule was smooth and glistening, and it was dark reddish-brown with large intermingled white to yellow patches. Its thin margins were rounded. The cut surface was brown, with similar indistinct yellow and red mottled areas. The brain weighed 450 gm. On section, after formalin fixation, it showed no anatomic lesion. The middle and internal ears were intact and free of gross exudate.

Heart.—The pericardium was smooth and glistening. The weight of the heart was not obtainable because of its attachment to the other thoracic structures. The myoeardium was firm and reddish brown. In situ, the right auricle appeared dilated and hypertrophied, with a notably dilated auricular cavity. The septal,

marginal, and infundibular cusps of the tricuspid valve were well formed and not thickened. The valve measured 5 cm. in circumference. The patent foramen ovale measured 1 cm. in diameter. The right ventricle was also dilated. It occupied the whole apex and measured 1 cm. in thickness. The columnae carneae were large, producing a marked fenestration of the wall of the chamber. The papillary muscles were hypertrophied. The pulmonary valve was intact and its sinus appeared dilated. The pulmonary artery was large, thick-walled, 3 cm. in circumference, and definitely dilated. The ductus arteriosus was widely patent, measuring 1.3 cm. in circumference, and was definitely dilated; it entered the aorta in its usual position.

The left auricle was small. The intima was smooth, pale gray and appeared thickened; a single pulmonary vein entered it on either side. The mitral valve was very hypoplastic and was 1 cm. in diameter. There was complete fusion of the leaflets, forming an irregular, pale gray thickening, covered with numerous granular, smooth, gray, pinhead elevations. The chordae tendinae were well defined, very delicate, and inserted directly into the myocardium, except for a rudimentary papillary muscle attached to the chordae of the posterior leaflet. The left ventricle formed a round cavity about 1.2 cm. in diameter, having a smooth, pearly-gray endocardial surface and a wall 8 mm. thick. The aortic valve was represented only by a dimpling at the base of this cavity, indicating the complete aortic atresia. The ascending aorta extended directly upward for 2.4 cm. as a thin, well-formed, but hypoplastic artery, only 4 mm. in circumference. It was continuous with the innominate artery, which was slightly larger than the aorta and much thicker-walled. The arch branched directly to the left, giving off normal-appearing left common carotid and subclavian branches.

The coronary arteries came off at the usual places. The left descending coronary artery extended down the left side of the interventricular septum, and the right appeared to anastomose with it on the opposite side. The apex of the very small left ventricle was situated 2.2 centimeters above the apex of the heart, which was therefore formed completely by the right ventricle.

Histologic Examination.—The right ventricle of the heart showed slight hypertrophy of the muscle fibers, with a thin endocardium. The left ventricle showed a hyaline, fibrous tissue thickening of the endocardium, with no cellular exudate. This fibrous tissue tended to surround the small vessels in the adjacent half of the myocardium and represented a sclerosing productive endocarditis which extended slightly into the adjacent myocardium. The sections of all other organs showed no anatomic lesion.

Anatomic Diagnosis.—Hypertrophy and dilatation of the right heart; patent ductus arteriosus and foramen ovale; hypoplasia of the left auricle and ventricle; hypoplasia of the mitral valve; *complete atresia of the aortic valve* and hypoplasia of the ascending aorta; productive endocarditis involving the entire left ventricle.

DISCUSSION

The appearance of the heart suggested that the anomalies might have been caused by a deviation to the left in the growth and fusion of the interventricular septum with the structures at the base. The right auricle and ventricle were therefore largely responsible for maintaining the systemic fetal circulation through the patent ductus and foramen ovale. Compensatory hypertrophy and dilatation of these chambers were the inevitable result.

In the normal course of the fetal circulation, the oxygenated blood from the placenta passes by the umbilical vein partly into the hepatic circulation, and the rest, by means of the ductus venosus, into the inferior vena cava and thence into the right auricle. The patent foramen ovale then allows the blood to flow successively into the left auricle and ventricle, whence it is propelled into the aorta. The blood from the superior vena cava passes through the right auricle into the right ventricle and thence by the ductus arteriosus into the aorta beyond the origin of the left subclavian artery. A small quantity also goes through the pulmonary artery. Normally, the ductus arteriosus closes soon after birth, and somewhat later a velum closes the foramen ovale.

Frequently, in atresia of the aortic valve, there is an associated anomaly (such as a septal defect), together with a widely patent ductus arteriosus. The latter occurred in this case, but there was no auricular or ventricular septal defect. It is also common in this group of defects which cause cyanosis to find the most severe type of congenital lesion. This results from the fact that there is no satisfactory collateral circulation except through the patent ductus arteriosus. Consequently, it is usual to find clinical evidences of marked cyanosis and a very considerable degree of dyspnea. However, in this case these features were entirely absent.

To understand why no cyanosis nor dyspnea appeared, it is necessary to visualize the exact method of circulation in this case. The oxygenated blood did, as in the normal fetal circulation, reach the left auricle and then proceed into the left ventricle. It could not be pumped by the left ventricle into the aorta because the valve of the latter was completely occluded. Actually, an eddy was probably set up and the blood swirled around in the left ventricle and back into the left auricle. Here some blood may, by back pressure, have been forced into the pulmonary veins. Thus the oxygenated blood that normally passes through the foramen ovale from the right auricle into the left heart and then into the aorta was in this case prevented from so doing by the atretic aortic valve. Hence the left heart was only a blind pocket which received a small current of blood, and the left ventricular systole prevented stasis and subsequent thrombus formation.

The oxygenated blood from the inferior vena cava had to mix with the more venous blood of the superior vena cava, which also entered the right auricle. The mixture passed into the right ventricle and on through the ductus arteriosus into the arch of the aorta and systemic circulation. It is to be assumed that this free mixing of the arterial and venous blood accounted for the absence of cyanosis. The aortic valve lesion cannot be regarded as the result of an acquired infection,

SUMMARY

These are the features of the case:

1. Congenital atresia of the aortic valve, which was a developmental defect of unknown etiology.
2. Complete absence of clinical signs of congenital heart disease.
3. A hypoplastic left ventricle with an endocarditis throughout the chamber.
4. Aortic atresia, shown to be very rare in a series of thirty-five congenital heart anomalies collected at the McGill Pathological Institute. Aortic stenosis is far more common. Still more frequent are interventricular septal defects, many of which are associated with incomplete rotation of the great vessels on the heart.

REFERENCES

1. Abbott, M. E.: Congenital Heart Disease, Reprinted from Nelson Looseleaf Medicine 4: 207, 1932.
2. Chase, W. H.: Persistent Cloaca and Tetralogy of Fallot, J. Tech. Methods, and Bull. Internat. Assoc. Med. Museums 12: 162, 1929.
3. Martens, G.: Zwei Fälle von Aortenatresie, Virchows Arch. f. path. Anat. 121: 322, 1890.
4. Moore, C. U.: Report of a Case of Congenital Anomaly of the Heart—Reptilian, Heart 8: 297, 1921.
5. Nelson, R.: Autopsy 60-32, Path. Records, Royal Victoria Hospital, 1932.
6. Philpott, N. W.: Congenital Atresia of Aortic Ring, Ann. Int. Med. 2: 422, 1928.
7. Shapiro, P. F.: Truncus Solitarius Pulmonalis, Arch. Path. 10: 671, 1930.

Department of Reviews and Abstracts

Selected Abstracts

Gregg, Donald E., and Dewald, Donald: The Immediate Effects of the Occlusion of the Coronary Veins on the Dynamics of the Coronary Circulation. *Am. J. Physiol.* 124: 444, 1938.

The phasic changes in venous pressure, peripheral coronary pressure, and arterial inflow in the heart have been studied by optical methods before and after acute cardiac venous ligation (coronary sinus or great cardiac vein).

The intravenous pressure rises from control values of about 10/2 mm. Hg to figures which during systole approach or exceed the aortic systolic and which rise in diastolic value to 20 to 40 mm. Hg.

The peripheral coronary pressure, simultaneously recorded, is elevated in the left coronary in like degree and has a contour and time relation similar to the venous pressure, although its ordinate values are generally slightly less. Probable explanations for these changes in venous and peripheral coronary pressure are advanced.

The arterial inflow into the left coronary is reduced considerably, while that into the right coronary is presumably not affected. Since, however, the left coronary inflow does not approach zero and the myocardium still contracts, it is believed that there are potent drainage channels still remaining. These are presumably venous, since if a left coronary ramus is now occluded the myocardium fails to contract even if the peripheral coronary is allowed to bleed.

Since it has been found that acute cardiac venous ligation does not prevent failure of contraction in a myocardial area whose coronary has been ligated and does reduce materially the left coronary arterial inflow, such a procedure cannot be regarded as a method of choice for encouraging the blood supply to such a potentially infarcted area.

AUTHORS.

Chen, K. K., Robbins, E. Brown, and Worth, Harold: The Significance of Sugar Component in the Molecule of Cardiac Glycosides. *J. Am. Pharm. A.* 27: 189, 1938.

The potency of five cardiac aglycones (strophanthidin, digoxigenin, digitoxigenin, calotropagenin and scillaridin A) has been carefully determined.

Each aglycone is less powerful on the heart than its parent glycoside—more pronounced in frogs than in cats. If the aglycone undergoes chemical changes during hydrolysis, as in the case of scillaridin A and calotropagenin, the cardiac action is reduced much further.

The emetic action of strophanthidin, digoxigenin and digitoxigenin, on the other hand, is greater than that of cymaridin, digoxin and digitoxin, respectively, molecule for molecule. When the structure of the aglycone is modified during hydrolysis, such as calotropagenin, the emetic action is diminished, but not to the same extent as the cardiac action.

The persistence of action among the aglycones is slight; that is, they are all rapidly eliminated from the circulation. This is particularly true with digitoxigenin in contrast with digitoxin.

Digitoxigenin caused a brief initial stimulation as manifested by convulsions, followed by marked depression of the central nervous system in cats and frogs. Digitoxin has no such action in corresponding doses.

AUTHORS.

Stead, Eugene A., Jr., and Kunkel, Paul: A Plethysmographic Method for the Quantitative Measurement of the Blood Flow in the Foot. *J. Clin. Investigation* 17: 711, 1938.

A plethysmographic method has been described for the quantitative measurement of the blood flow in the foot. With a standard correction for the inertia of the plethysmograph-bellows system, the instrumental error was found to be ± 3 per cent. The plethysmograph is also useful in the study of the vasomotor reactions of the vessels of the foot.

AUTHORS.

Nylin, S., and Sällström, T.: Three Synchronised Leads Between Fixed Points on the Heart Projection in the Chest Wall. *Acta med. Scandinav.* 96: 1, 1938.

A study of chest leads was made according to the Wood-Wolferth technique and needle electrodes. The electrodes were placed in certain locations determined after x-ray examination of the heart. In normal persons they found the chest leads remarkably constant. In cases of acute coronary occlusion and of coronary disease changes were found which were consistent with those published in the American literature.

JENSEN.

Bock, H.: The Q-T Interval in Diphtheria Affecting Children. *Ztschr. f. Kreislaufforsch.* 30: 761, 1938.

Twelve hundred electrocardiograms on 300 diphtheria patients were studied. It was found that the Q-T interval lengthened in diphtheria. This gives evidence of myocardial involvement. Extreme prolongation is a sign of bad prognosis.

KATZ.

Damin, Bustave J., and Moore, Robert A.: Cardiac Muscle in Idiopathic Hypertrophy of the Heart in Infancy and in Normal Growth. *Arch. Path.* 27: 122, 1939.

In a case of idiopathic hypertrophy of the heart in an infant 53 days old the apparent number of muscle fibers was increased above the normal, but there was no increase in the number of nuclei.

A study of the hearts of an infant 2 months old, a child 8 years old, and an adult indicates that there is an increase in the total number of fibers and in that of nuclei during normal growth.

AUTHORS.

O'Farrell, P. T.: The Clinical Diagnosis of Congenital Heart Disease. *Irish J. M. Sc.* 153: 597, 1938.

The author discusses the clinical signs and diagnosis of congenital lesions of the heart which are compatible with life, and which present fairly distinct clinical or radiologic features. The approach to the clinical diagnosis should follow a definite

plan. The first step which may be relatively easy is to establish the existence of a congenital lesion by ruling out the possibility of acquired disease. The next step, which is much more problematical, is to define the precise anatomic lesion or lesions. In the majority of cases only an approximate diagnosis can be attempted. There are certain criteria which are extremely helpful and he discusses these, each briefly.

There is also a discussion of each of the common clinical types of lesions with the symptoms and signs usually associated with each one.

Altogether, the article presents a most interesting and intelligent review of this subject.

McCulloch.

Bell, G. H.: The Human Foetal Electrocardiogram. *J. Obst. & Gynaec. Brit. Emp.* 45: 802, 1938.

Using a thermionic valve electrocardiograph, capable of very high amplification, the electrocardiograms obtained when leads are taken from the abdomen of pregnant women show in some cases waves which are almost certainly fetal in origin. The evidence supporting the fetal origin is that the direction of the fetal deflection depends on the presentation (vertex or breech) and in a case of a twin pregnancy two sets of deflections were obtained.

Of thirty-three cases examined in the last two months of pregnancy about one-third showed positive results, but the other two-thirds did not show any wave on the electrocardiogram which could be definitely recognized as fetal.

It is suggested that the failure to secure positive results in all cases is due partly to differences in the electrical properties of the abdominal wall, and partly to the electrical disturbances produced by the abdominal muscles, and not to insufficient sensitivity of the apparatus or to differences between the fetuses.

AUTHOR.

Coburn, Alvin F., and Pauli, Ruth H.: The Significance of Prolonged Streptococcal Antibody Development in Rheumatic Fever. *J. Clin. Investigation* 18: 141, 1939.

Findings are presented which support the view that prolonged increases in streptococcal antibody, such as are observed in rheumatic fever, signify subclinical activity of hemolytic streptococcus.

AUTHORS.

Westphal, K., and Sievert, C.: Concerning the Stimulating Material of Genuine Hypertension. *Ztschr. f. Klin. Med.* 133: 223, 1937-38.

1. Endocrine disharmony in genuine hypertension—the occasion to hunt for and to find the stimulative material (p. 223): A number of patients who exhibit “genuine hypertension” associated with a variety of the stigmas of endocrine disturbances are described. They fall, chiefly, into two groups: adolescents with dystrophia adiposogenitalis; and middle-aged obese men with feminine habitus and loss of libido. They note, also, that when two of the adolescent cases without hypertension were treated with pituitary (hypobolan) and thyroid extract, they developed a hypertension. Finally, analysis of 100 cases of hypertension revealed some evidence of endocrine disturbance in all but eleven instances.

These observations led them to look for a pressor substance in the blood of hypertensive patients by the method of Anselmino and Hoffmann (ultrafiltration). A substance was found which regularly gave a rise in arterial pressure of rabbits on intramuscular injection, which persisted usually for as long as an hour.

2. Results of the study of pressor substances in the blood of genuine, renal, and malignant hypertension (p. 248): The pressor substance was found present in all but 15 of 102 instances of "genuine hypertension" in about the same proportion of cases with malignant sclerosis and in about half of those with acute nephritis. Several instances are recorded wherein the amount of pressor substance varied with the level of blood pressure.

3. The technique of demonstrating the pressor substance, its physicochemical properties as well as proof of the cortico-tropic substance (p. 261): The substance resembles Tonephin (posterior pituitary Extract I-g. Farbenindustrie A.-G.) in some ways (destroyed easily by alkali and ultraviolet light) but differs in others (lacks antidiuretic action and is active intramuscularly). The authors seem to believe it to be similar. Besides the pressor action, two other actions of the ultrafiltrate were shown to be present by their effect upon the size and lipid content of the adrenal gland—the first was found to be identical with the cortico-tropic hormone of the anterior pituitary and the second was thought to be similar to the adrenal-tropic hormone.

4. Studies concerning the circulatory action of the pressor substance from the blood of genuine hypertension (p. 277): The pressor effect is shown to be peripheral in action.

5. Studies concerning the acute influence of the pressor substance upon blood pressure, adrenal secretion, and chronic studies of blood pressure (p. 291): Daily injections of the ultrafiltrate of blood from hypertensive patients give rise to chronic hypertension and increased lipid content of the adrenal glands in rabbits. Neither of these phenomena occurs when the ultrafiltrate is obtained from normal blood. A single injection gives rise to a hyperglycemia which persists for seven or eight hours and which is abolished by removal of the adrenal glands.

The symbiosis of the cortex and medulla of the adrenal from the point of view of histological studies of the adrenals under different experimental and pathological conditions and especially in genuine hypertension (p. 311).

6. From histologic studies of adrenals in experimental and "genuine" hypertension, the conclusion is reached that both medulla and cortex are affected.

7. Genuine hypertension as a primary endocrine disease (p. 342). Three patients with hypertension were subjected to removal of one adrenal gland and implantation of three calves' hypophyses. Level of blood pressure for all three fell promptly but the records show only a few weeks of postoperative follow-up examinations. Also several patients with circulatory collapse (pneumonia, etc.) and chronic hypotension were treated with whole blood (transfusions) or ultrafiltrate of blood from hypertensive patients with rise in arterial pressure and increase in general strength.

From this series of studies the authors conclude that hypertension is primarily an endocrine disturbance.

STEELE.

Williams, John R., Jr., Wegria, R., and Harrison, T. R.: Relation of Renal Pressor Substance to Hypertension of Hydronephrotic Rats. *Arch. Int. Med.* 62: 805, 1938.

Rats with spontaneous bilateral hydronephrosis display well-marked elevation of blood pressure. Rats with spontaneous unilateral hydronephrosis may or may not have an elevated blood pressure. Hydronephrotic rats respond to the injection of renal extract with a more marked rise in blood pressure than do normal rats of similar size and age. Extract of the abnormal kidneys of rats with spontaneous unilateral hydronephrosis produces greater pressor effects than does a similar extract of the normal kidneys of the same rats. Extract of the kidneys of rats with spontaneous bilateral hydronephrosis causes a greater rise in blood pressure than does extract of the kidneys of normal rats.

Ligation of one ureter for a period of several days causes slight hydronephrosis but no constant rise in blood pressure. After unilateral ureteral ligation the sensitivity of rats to renal pressor substance is somewhat greater than that of normal animals. Extract of the kidney rendered hydronephrotic by ligation of the ureter has a greater pressor effect than does a similar extract of the opposite normal kidney of the same animal.

AUTHOR.

Langendorf, R., and Pick, A.: On the Diagnosis of Myocardial Infarct With the Aid of Chest Wall Leads. *Acta med. Scandinav.* 96: 80, 1938.

Little work has been done on the reappearance of the preintrinsic positive deflection in chest leads following posterior coronary occlusions. There have been discussions of the negative deflection which frequently precedes the preintrinsic positive deflection. Most authors consider that such a deflection, if big, has a similar significance as has absence of the preintrinsic posterior deflection. Normally this wave is always less than 0.3 millivolt. When it becomes greater than this, the authors consider it of great diagnostic importance. Often, however, it is important to change the position of the pick-up electrode to various areas between the apex and the left sternal border. Sometimes the preintrinsic position deflection returns before the T-wave changes return to normal. Sometimes it is present, though small, in the presence of large infarcts. This fact somewhat impairs the value of the chest lead. Differences in curves originating from different sites of application of electrodes are brought about by the use of large electrodes.

AUTHORS.

Schwab, Edward H., and Curb, Dolph L.: A Note on the Diagnosis of Hypertensive Cardiovascular Disease Without Hypertension. *J. Lab. and Clin. Med.* 24: 125, 1938.

The middle-aged patient who presents moderate to marked cardiac enlargement and who does not have hypertension or significant vascular lesions provides an interesting diagnostic problem from the etiological standpoint. The cause of the cardiac enlargement in these patients is usually obscure. O'Hare and his associates have emphasized that under such circumstances the patient probably has had a previous hypertension. Although it is probable that hypertension has been present in such patients, a definite history of this is usually difficult to confirm. It was considered that these suspected hypertensive cardiopaths might still retain the hypersensitivity of the vasomotor apparatus to stimulation even though their blood pressure was no longer elevated. The cold pressor test of Hines and Brown was utilized in testing the vasomotor reactivity of these patients. Seven subjects with known previous hypertensive vascular disease in whom the blood pressure had fallen to normal or subnormal were subjected to the cold pressor test. Five of the seven patients gave a marked hypertensive type of response. One gave a borderline type of response and one an essentially normal response. In the patient with the borderline response it was felt that a primary nephritis might have been the etiological factor of the hypertension. The findings in this small group suggest that the application of the cold pressor test to patients of this type would materially aid in clarification of the etiological cardiac diagnosis.

HINES.

Major, Ralph H.: Blood "Guanidine" in Arterial Hypertension: A Review of Eight Hundred Cases. *Arch. Int. Med.* 62: 946, 1938.

The "guanidine" content of the blood of 800 patients with hypertension observed over a period of ten years was increased in 43 per cent of the entire series and in 32 per cent of those whose blood had a nonprotein nitrogen content not exceeding 40 mg. per 100 c.c.

NAIDE.

Mills, John H., and Horton, Bayard T.: **Clinical Aspects of Aneurysm.** Arch. Int. Med. 62: 949, 1938.

A total of 596 cases of aneurysm were recorded at the Mayo Clinic in the years 1925 to 1935, inclusive. In this series of cases, 143 of the aneurysms were intracranial, 339 were intrathoracic, 80 were intra-abdominal, 21 involved the extremities, and 13 were of a miscellaneous character. Syphilis was present in 3.5 per cent of the cases of intracranial aneurysm, in 70 per cent of the cases of thoracic aneurysm, in 8.8 per cent of the cases of intra-abdominal aneurysm, in 9.5 per cent of the cases of aneurysm of an extremity, and in 7.7 per cent of the miscellaneous cases of aneurysm. In a total of 172, or 28.9 per cent, of the 596 cases the diagnosis of aneurysm was verified at operation or necropsy.

AUTHORS.

Boland, Edward W., and Willus, Fredrick A.: **Changes in the Liver Produced by Chronic Passive Congestion.** Arch. Int. Med. 62: 723, 1938.

The usual histopathologic picture of the liver in cases of prolonged or recurrent episodes of congestive heart failure is that of central lobular atrophy, or necrosis, or both. Condensation of reticulum and thickening may or may not be present.

The presence of condensation of reticulum alone does not warrant the use of the term cardiac cirrhosis.

True cirrhosis, developing in the course of congestive heart failure, does occur but is rare. No definite criteria were elicited from this study whereby the development or presence of cardiac cirrhosis can be recognized clinically.

AUTHORS.

Epstein, Bernhard S.: **The Visualization of the Aorta by the Method of Roentgenographic Overpenetration.** Am. J. Roentgenol. 40: 396, 1938.

The technique of overpenetration has been useful in outlining the cardiac shadow in patients with opacities in the adjacent lung fields. Extension of the heart shadow below the diaphragm may be demonstrated. Shadows of double density on the right cardiac border in instances where the left auricle approaches the right border are sometimes seen. The contour of the thoracic spine can be determined, and instances in which a thoracic deformity was of differential diagnostic import have been noted. It is also possible to visualize the trachea and main bronchi.

AUTHOR.

Grandgérard, R., and Heim de Balsac, R.: **The Primary Arterial Tree of the Lungs and the Cortical Destination of Its Ramification.** Presse méd. 45: 444, 1937.

Through visualization by Lucien's method the arterial tree in the lungs is subdivided into various sections. The notion of areas of ventilation of the lungs added to the knowledge of the elements of the distribution of vessels is useful in the localization of lesions of the lung even after projection on to the single plane of the x-ray film.

JENSEN.

Goldblatt, Harry: **Experimental Observations on the Surgical Treatment of Hypertension.** Surgery 4: 483, 1938.

The effect of experimental occlusion of the renal artery on the production of hypertension is reviewed and discussed.

The author then discusses the application of this observation to hypertension in humans. Whether renal decapsulation and other surgical procedures for the establishment of collateral circulation to the kidney would be effective in either essential hypertension or other types, must be worked out. The author believes there is probably more justification on an experimental basis for the surgical procedure than there has been for some of the others that have already been practiced. The cases in which the surgical production of accessory circulation would be most effective would be those in which the hypertension is due to sclerosis of the main renal arteries alone, or their very large branches. The difficulty of making a diagnosis of this condition is obvious so that unless the method could be applied to essential hypertension associated with renal arteriolar sclerosis, the procedure would be of greatly restricted value.

McCULLOCH.

Weitzmann, G.: (Abstracted From Notes.) Report of the Fourteenth Meeting of the German Pharmacological Society April 24 to 28, 1938. *Ztschr. f. Kreislaufforsch.* 30: 736, 1938.

P. Holtz, Greifswald: "Formation of a Pressor Substance From Dioxyphe-nylalanin by Animal Tissues." Kidney extract forms a pressor substance from dioxyphe-nylalanin when the medium is made anoxemic. The substance appears to be oxytyramin.

Rühl and Thaddea, Berlin: "Lactic Acid in the Heart-Lung Preparation Following Caffeine." Caffeine, 0.15-0.35 gm., makes the heart in the heart-lung preparation insufficient and at the same time lactic acid accumulates in the blood. This differs from other types of damage to the heart, viz., pernocton, histamine, or N_2 , where no interference with lactic acid utilization is seen.

Kuschinsky, Berlin: "Water Balance." The quantity of antidiuretic hormone of the posterior pituitary gland was determined in male rats. Excess water (one-twentieth body weight daily for one week) was found to have no effect on this determination. When, however, 4 per cent NaCl was added, the hormone was decreased in amount on the day following. The same decrease was found to occur after novasurol, but theophyllin had no such effect.

Hildebrandt, Osterwald, Giessen: "Strophanthin on Coronary Flow." In the intact anesthetized animal, coronary flow was studied by means of a Rein stromuhr. It was found that doses of strophanthin equivalent to 0.15 to 0.5 mg. for man had no direct effect on coronary blood flow to the right coronary artery. The coronary flow changes following strophanthin paralleled the changes in peripheral flow.

Hahn, Cologne: "Digitalis Sensitivity When Blood Calcium Is Elevated." The lethal dose of strophanthin is decreased when blood calcium is raised by calcium chloride injections.

Hesscl, Frankfort: "Experimental Observations on the Pathogenesis of Renal Hypertension." Injections of venous blood from the ischemic kidneys of animals (rabbit and dog) having developed chronic hypertension, cause a rise in pressure in the recipient animal. Arterial blood or venous blood from nonischemic kidneys does not have this action. Renin is the substance to which this pressor action is attributed. This material causes a decrease in renal flow and so can establish the mechanism whereby hypertension is established and maintained. Removal of the kidneys in animals rendered hypertensive by chronic injections of renin leads to a fall in blood pressure. Renin thus appears to be responsible for the vicious cycle of hypertension.

KATZ.

American Heart Association, Inc.

RADIO CITY

50 WEST 50TH STREET, NEW YORK, N. Y.

DR. WILLIAM J. KERR
President

DR. WILLIAM D. STROUD
Vice-President

DR. HOWARD B. SPRAGUE
Secretary

DR. WALTER W. HAMBURGER
Treasurer

BOARD OF DIRECTORS

DR. T. HOMER COFFEN Portland, Ore.
DR. CLARENCE DE LA CHAPELLE New York City

DR. WALTER W. HAMBURGER Chicago
DR. GEORGE R. HERRMANN Galveston

DR. EMMET F. HORINE Louisville

*DR. WILLIAM J. KERR San Francisco

*DR. EMANUEL LIBMAN New York City

DR. HUGH McCULLOCH St. Louis

*DR. GILBERT MARQUARDT Chicago

*DR. H. M. MARVIN New Haven

*DR. EDWIN P. MAYNARD, JR. Brooklyn

DR. JONATHAN MEAKINS Montreal

*DR. FRANKLIN NUZUM Santa Barbara

DR. STEWART R. ROBERTS Atlanta

DR. WILLIAM H. ROBEY Boston

DR. ROY W. SCOTT Cleveland

*DR. HOWARD B. SPRAGUE Boston

*DR. WILLIAM D. STROUD Philadelphia

DR. LOUIS VIKO Salt Lake City

DR. HOWARD F. WEST Los Angeles

DR. PAUL D. WHITE Boston

DR. FRANK N. WILSON Ann Arbor

DR. CHARLES C. WOLFERTH Philadelphia

*DR. IRVING S. WRIGHT New York City

*DR. WALLACE M. YATER Washington, D. C.

DR. H. M. MARVIN, *Acting Executive Secretary*

GERTRUDE P. WOOD, *Office Secretary*

TELEPHONE CIRCLE 5-8000

THE American Heart Association, sponsor of the first International Health Broadcast, stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is \$5.00 a year and journal membership at \$10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

**Executive Committee.*

The American Heart Journal

VOL. 17

MAY, 1939

No. 5

Original Communications

A COMPARISON OF THE CHANGES IN THE HUMAN ELECTRO-CARDIOGRAM FOLLOWING THE ADMINISTRATION OF STROPHANTHIN AND ACETYLCHOLINE AND DURING VAGAL STIMULATION*†

NIELS A. NIELSEN, M.D., AND MOGENS TRIER, M.D.
COPENHAGEN, DENMARK

IN A previous work it was shown that the cardio-inhibitory vagal effect caused by the digitalis substances is most likely due solely to a sensitization of the heart muscle to the normal vagus tone (Abdon and Nielsen¹). This was combined with Loewi's supposition that acetylcholine is the vagus substance; and after it had been demonstrated upon the isolated hearts of frogs and rabbits that following the administration of strophanthin the same dose of acetylcholine produced a more pronounced bradycardia than before strophanthin was given, the supposition that the digitalis bradycardia is due to a sensitization of the heart muscle to acetylcholine was considered justifiable (Abdon and Nielsen²).

Soon afterward, Gremels³ (1937), experimenting with isolated frogs' hearts, found an augmentation of the chronotropic effect of acetylcholine following the administration of strophanthin, and he showed further that strophanthin increases the effect of acetylcholine on the oxygen consumption and mechanical efficiency of the heart-lung preparation.

It therefore seemed natural to inquire whether any of the other effects of the digitalis substances are due to a sensitization of the heart muscle to acetylcholine.

The digitalis substances cause characteristic changes in the electrocardiogram. If the administration of acetylcholine, as well as vagal stimulation, causes similar changes, those which occur after the administration of digitalis are to be explained by a sensitization of the heart muscle to the acetylcholine liberated by the normal vagal tone.

*From the Medical Clinic B, University of Copenhagen (Chief Physician; Professor E. Warburg, M.D.).

†Aided by a grant (to N. A. N.) from the P. Carl Petersens Fond.

Received for publication June 17, 1938.

A direct comparison of the changes in the electrocardiogram brought about in these different ways does not seem to have been made previously, but separate investigations, both on animals and man, have been reported.

Experiments on Man.—The changes in the electrocardiogram of normal adults following the administration of digitalis have been described by Larsen, Neukirch and Nielsen⁴ (1937), who concluded from previous investigations and their own results that the most important changes are relative shortening of the electrical systole, depression of the S-T interval, and flattening of the T-waves; bradycardia occurred in only a little more than half the cases. Moreover, it may be added that in one-third of the healthy persons whom they examined, Routier and Puddu⁵ (1935) found lower P-waves in Leads II and III after the administration of digitalis. In all of these experiments digitalis itself was used. Regarding strophanthin, Cohn and Levy⁶ (1920) state that the effect on the T-waves is only slight or does not appear at all. Kahlson⁷ (1928) found that the T-waves were flattened after the intravenous injection of strophanthin, whilst Aschenbrenner⁸ (1936) maintained that strophanthin does not cause any changes in the T-waves.

The effect of acetylcholine has been studied by Carmichael and Fraser⁹ (1933), who state that in four adults the intravenous injection of this drug caused a slowing of the heart rate, but did not otherwise influence the electrocardiogram.

Vagal stimulation in man is obtained reflexly by pressure on the carotid sinus. Weiss and Baker¹⁰ (1933) found that this procedure caused bradycardia and sometimes complete standstill of the heart; in some cases the electrocardiogram showed auriculoventricular block, and in a few instances ventricular extrasystoles. Nathanson¹¹ (1933) obtained similar results.

Animal Experiments.—Inasmuch as the effect of the administration of strophanthin and acetylcholine, as well as that of vagal stimulation, has been studied only in dogs, the discussion will be limited to this animal.

According to Selenin¹² (1912), the administration of digitoxin causes bradycardia, auriculoventricular block, and an increase in the size of the T-waves, whilst Bickel and Pawlow¹³ (1913) found that the T-waves became lower after the administration of strophanthin, and that bradycardia occurred in only one of four dogs. Cohn and Stewart¹⁴ (1928) administered tincture of digitalis and digifolin and obtained changes in the T-waves and commonly bradycardia. Lastly, Brams¹⁵ (1929) found that different preparations of digitalis caused bradycardia and sometimes delayed auriculoventricular conduction, but that the changes in the T-waves were inconstant.

Goldenberg and Rothberger¹⁶ (1934) have examined the effect of acetylcholine on the electrocardiograms of dogs. They state that the first changes are found in the P-waves; later, auriculoventricular block and sometimes depression of the S-T interval appear, but bradycardia

is seldom seen. The tables of the paper, however, show that in several experiments there was a decided early decrease in cardiac rate.

Vagal stimulation has most often been electrical. There is some disagreement about the results (Einthoven,¹⁷ 1908; Hering,¹⁸ 1909; Rothberger and Winterberg,¹⁹ 1910; Goldenberg and Rothberger,¹⁶ 1934). The disagreement is probably due to the fact that this method of stimulation also involves nerves belonging to the accelerans. Here we can consider, therefore, only the experiments in which the stimulation has been reflex, caused by changing the pressure in the carotid sinus. Kisch and Sakai²⁰ (1923) produced tachycardia by compressing the carotids of dogs. At the moment pressure was released, and the pressure inside the carotid sinus increased, the cardiac rate again became slow. The paper gives an illustration of an electrocardiogram taken during such an experiment which shows that the P-waves grew lower during the period of bradycardia.

If the experimental results cited above be compared, it may be seen that there is a certain resemblance among the electrocardiographic changes obtained in these different ways, but that they are not by any means in complete agreement. This may perhaps be explained by the fact that the three different kinds of experiments were not carried out on the same subject, so that the dissimilarities could be due to individual variations in mode of reaction. Therefore, in our investigation the changes in the electrocardiogram which occurred following the administration of strophanthin and of acetylcholine and during vagal stimulation caused by pressure on the carotid sinus or on the eyeball were compared in successive experiments on the same person.

TECHNIQUE

The persons used for the experiments were male adults who did not present any subjective or objective signs of disease of the circulatory system. There were no auscultatory, roentgenologic, or electrocardiographic abnormalities, and the blood pressure was normal in each instance.

During the examination the subject lay in bed. The experiments with strophanthin were carried out in the morning. A light breakfast was given, after which the subject rested for about an hour in the room in which the experiment was to be done. It was first ascertained that the heart rate was constant.

The electrocardiograms were obtained by means of an amplifier apparatus which allows all three leads to be taken simultaneously, Lead III being about half the size of the other two. Each electrocardiogram was standardized so that the introduction of 1 mv. caused a deflection of 20 to 23 mm. The time marking was 0.2 and 0.05 sec. and the speed of the film 8 to 9 cm. per sec. In Lead II the measurement of the intervals was accurate within ± 0.003 sec. In the experiments in which acetylcholine was injected or pressure exerted on the carotid sinus, the last three complexes before and the first three after the onset of bradycardia were measured, and in the strophanthin experiments the mean of five beats before and five beats after injection was calculated (Table I).

Strophanthin was given intravenously in an aqueous solution of 1:2000 (sol. g-strophanthini, *Pharmacopea Danica*, 1933). The injection lasted about one minute.

A 5 per cent solution of acetylcholine chloride (Merck) was prepared before each experiment. It was injected intravenously as quickly as possible; the first dose was

0.2 c.c., and the size of each succeeding dose was increased by 0.1 c.c. until an effect was obtained.

The vagus was stimulated reflexly in four of the subjects by pressure on the carotid sinus, and in the fifth by pressure on the eyeball.

Inasmuch as the effect of strophanthin is protracted, the experiments were carried out in the following order: (1) Pressure on the carotid sinus, (2) injection of acetylcholine, and (3) injection of strophanthin.

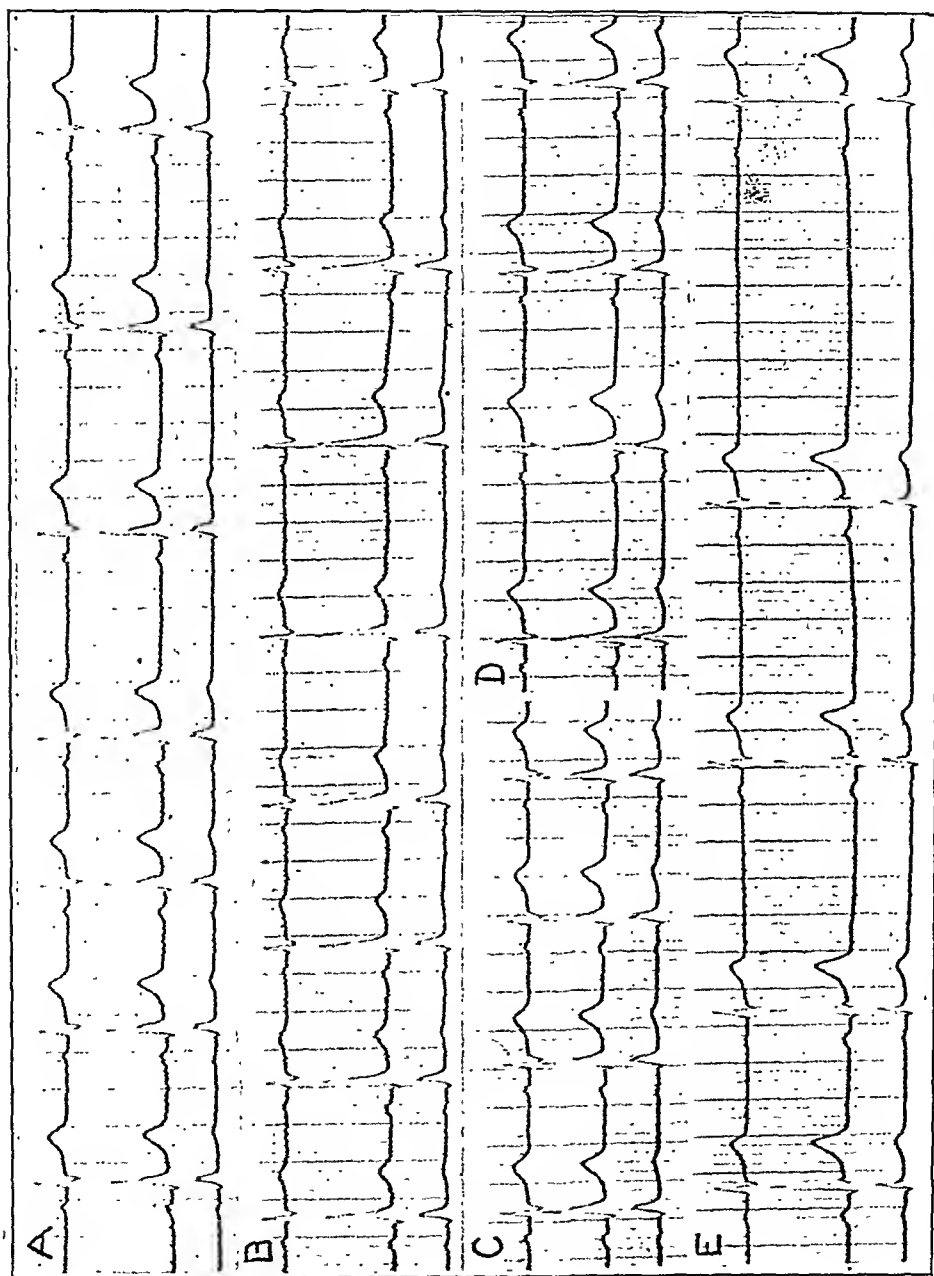


Fig. 1.—Electrocardiograms made during vagal stimulation, during injection of acetylcholine, and before and after injection of strophanthin. A, Vagal stimulation (pressure on carotid sinus). B, Injection of acetylcholine. C, Before injection of strophanthin. D, After injection of strophanthin. A, B, C and D are from the same person (Subject 1). E, vagal stimulation (pressure on eyeball) in another person (Subject 5).

RESULTS

The results are summarized in Table I. This table shows that during pressure on the carotid sinus there was a pronounced bradycardia, and at this time the electrical systole (Q-T interval) was either unchanged or so little prolonged that it was obviously relatively shortened (Fig.

TABLE I

CHANGES IN THE ELECTROCARDIOGRAM DURING PRESSURE ON THE CAROTID SINUS OR THE EYEBALL, FOLLOWING INJECTION OF ACETYLCHOLINE AND OF STROPHANTHIN

SUB- JECT	EXPERIMENT	HEART BEAT	R-R ₂ IN SEC.	FOL- LOWING Q-T ₂ IN SEC.	CHANGES IN OTHER PARTS OF ELECTROCARDIOGRAM
1.	Pressure on carotid sinus	3 beats immedi- ately before	0.748 0.808	0.349 0.357	
		pressure	0.786	0.357	
		3 beats during pressure	0.994 0.946 0.976	0.361 0.367 0.373	None
	Pressure on carotid sinus	3 beats immedi- ately before	0.820 0.787	0.388 0.388	
		pressure	0.793	0.391	
		3 beats during pressure	1.110 1.099 1.075	0.391 0.391 0.402	P ₂ lower and more pointed, P ₃ from positive to negative
	Acetylcholine, 15 mg. intravenously	3 beats immedi- ately before	0.911 0.905	0.393 0.387	
		injection	0.863	0.390	
		3 beats immedi- ately after in- jection	0.929 1.018 0.946	0.387 0.387 0.393	None
	Acetylcholine, 35 mg. intravenously	3 beats immedi- ately before	0.862 0.890	0.369 0.372	
		injection	0.862	0.372	
		3 beats immedi- ately after injection	1.156 1.207 1.100	0.375 0.378 0.378	P ₂ lower and more pointed, P ₃ lower
2.	Strophanthin, 0.25 mg. intravenously	Average of 5 beats before injection	0.796	0.366	
		Average of 5 beats 12 min. after inj.	0.879	0.366	None
		Average of 5 beats before injection	0.766	0.380	
	Strophanthin, 0.50 mg. intravenously	Average of 5 beats 5 min. after inj.	0.968	0.386	P ₂ lower and more pointed, P ₃ from positive to negative
		3 beats immedi- ately before	1.012 1.073	0.393 0.396	
		pressure	1.067	0.387	
	Acetylcholine, 20 mg. intravenously	3 beats during pressure	1.311 1.262 1.201	0.387 0.396 0.393	None
		3 beats immedi- ately before	1.009 1.021	0.388 0.385	
		injection	1.024	0.394	
	Strophanthin, 0.50 mg. intravenously	3 beats immedi- ately after in- jection	1.810 2.795 1.290	0.398 0.391 0.406	P ₂ higher, P ₃ from diphasic to positive
		Average of 5 beats before injection	0.816	0.350	
		Average of 5 beats 12 min. after inj.	0.879	0.347	None

TABLE I—CONT'D

SUB- JECT	← EXPERIMENT	HEART BEAT	R-R ₂ IN SEC.	FOL- LOWING Q-T ₂ IN SEC.	CHANGES IN OTHER PARTS OF ELECTROCARDIOGRAM
3.	Pressure on carotid sinus	3 beats immedi- ately before	0.799	0.364	
		pressure	0.799	0.362	
			0.775	0.356	
		3 beats during pressure	1.120	0.362	P ₂ and P ₃ more pointed
	Acetylcholine, 35 mg. intravenously	3 beats immedi- ately before	0.600	0.329	
		injection	0.603	0.326	
			0.609	0.320	
		3 beats immedi- ately after in- jection	0.845	0.333	P ₂ more pointed, P ₃ more pointed and lower
	Strophanthin, 0.25 mg. intravenously	Average of 5 beats before injection	0.956	0.338	
			0.956	0.338	
		Average of 5 beats 8 min. after inj.	0.740	0.346	
			0.893	0.351	P ₂ more pointed
4.	Pressure on carotid sinus	2 beats immedi- ately before	0.694	0.375	
		pressure	0.742	0.380	
		3 beats during pressure	1.002	0.380	P ₂ lower, P ₃ from positive to negative
			1.008	0.375	
	Acetylcholine, 30 mg. intravenously		0.980	0.386	
		3 beats immedi- ately before	0.838	0.371	
		injection	0.838	0.374	
			0.838	0.374	
		3 beats immedi- ately after in- jection	0.906	?	None
			0.974	0.375	
			0.971	0.372	
5.	Pressure on eyeball	Average of 5 beats before injection	0.814	0.387	
			1.033	0.396	P ₂ narrower
		Average of 5 beats 15 min. after inj.			
		3 beats immedi- ately before		0.364	P-Q ₂ = 0.167
		pressure	0.962	0.370	P-Q ₂ = 0.167
			0.962	0.370	P-Q ₂ = 0.170
		3 beats during pressure	1.349	0.375	P-Q ₂ = 0.167 P ₂ and P ₃
			1.393	0.372	P-Q ₂ = 0.191 lower and lower
			2.182	0.380	P-Q ₂ = 0.287
	Acetylcholine, 32.5 mg. intravenously	3 beats immedi- ately before	0.829	0.351	
		injection	0.781	0.347	
			0.784	0.347	
		3 beats immedi- ately after in- jection	0.927	0.347	None
	Strophanthin, 0.25 mg. intravenously		0.994	0.351	
			0.963	0.351	
		Average of 5 beats before injection	0.870	0.354	
		Average of 5 beats 12 min. after inj.	1.004	0.363	None

1A). When bradycardia was pronounced the P-waves were flattened in Leads II and III, but no changes occurred when the bradycardia was less pronounced. In one experiment on Subject 1 there was moderate bradycardia without changes in the P-waves, but when, in another experiment, the bradycardia was more pronounced, the P-waves were flattened in Leads II and III (Table I). Subject 5 responded to pressure on the eyeball with a great decrease in cardiac rate, accompanied by flattening of the P-waves in Leads II and III, and the slower the rate, the greater the flattening. Simultaneously, the auriculoventricular conduction was delayed in proportion to the decrease in cardiac rate (Fig. 1E). The other waves and intervals of the electrocardiogram did not change.

The intravenous injection of acetylcholine was followed by the same changes, except that auriculoventricular conduction was never delayed (Fig. 1B). As in the experiment with carotid sinus stimulation, the changes in the P-waves did not appear until the bradycardia became pronounced (Table I, Subject 1). In one subject (No. 2) the P-waves became higher, but in all of the others they grew smaller.

The injection of strophanthin was followed, after a very short interval, in some cases less than one minute, by a definite decrease in cardiac rate which became more pronounced during the succeeding minutes; the Q-T interval either remained unchanged or was inconsiderably prolonged, i.e., there was a relative shortening of electrical systole (Fig. 1C and D). The changes in the P-waves were the same as those which occurred after carotid pressure and the injection of acetylcholine (flattening in Leads II and III when the bradycardia was pronounced, no change when the rate was only slightly decreased [Table I, Subject 1]). In none of the cases were other changes found, especially the T-waves were not altered, neither was auriculoventricular conduction delayed, within twenty-four hours after the injection.

DISCUSSION

The changes in the electrocardiogram during pressure on the carotid sinus and the eyeball (bradycardia, relative shortening of the Q-T interval, flattening of the P-waves in Leads II and III in cases of pronounced bradycardia, and a single instance of delayed auriculoventricular conduction) were essentially the same as those observed by previous investigators. It is true that relative shortening of the electrical systole has not been mentioned previously, but it is to be seen in the electrocardiograms which have been published. The extrasystoles which others have observed did not occur in our experiments, possibly because of individually different modes of response.

The changes following intravenous administration of acetylcholine corresponded to those produced by pressure on the carotid sinus and eyeball, except that delayed auriculoventricular conduction was not observed. This was probably because of the small amounts of acetylcholine used, for it has been shown in animal experiments that it may have this effect.

The changes following the intravenous administration of strophanthin corresponded to those produced by acetylcholine, viz., bradycardia, relative shortening of electrical systole, and, when the bradycardia was pronounced, flattening of the P-waves in Leads II and III. These results agree with those obtained by investigators who have used digitalis, except that with digitalis there were also changes in the T-waves, and sometimes delayed auriculoventricular conduction and extrasystoles. It has previously been demonstrated that the T-waves are not affected by the administration of strophanthin. The fact that the other changes were not observed in the present experiments may be explained by the well-known individual variations in response to digitalis substances, or by assuming that the doses of strophanthin which were used were too small to effect them.

It is seen that in the same subject the electrocardiographic responses to strophanthin, acetylcholine, and vagal stimulation were identical.

Goldenberg and Rothberger¹⁶ have compared the electrocardiographic changes following the administration of acetylcholine and vagal stimulation in dogs, cats, and rabbits, and have not found complete agreement, but nevertheless they draw the conclusion "dass der Vagusstoff mit dem Acetylcholin identisch ist oder ihm wenigstens sehr nahe steht." As they themselves point out, the difference is most likely due to the fact that electrical stimulation of the vagus also stimulates the nerves belonging to the accelerans. In the experiments presented here, the electrocardiographic changes following acetylcholine and reflex augmentation of the vagal tone have been compared and found to be identical, which speaks in favor of the supposition that acetylcholine is the vagus substance.

It was mentioned in the introduction that the bradycardia following the administration of digitalis is supposed to be caused by a sensitization of the heart muscle to acetylcholine. Further, it was stated that strophanthin increases the effect of acetylcholine on the oxygen consumption and mechanical efficiency of the heart-lung preparation. It was therefore considered natural to inquire whether other effects of digitalis might be explained by acetylcholine sensitization. The present investigation demonstrates that the changes occurring in the electrocardiogram following the injection of acetylcholine and strophanthin in successive experiments on the same person are identical. It therefore seems justifiable to assume that the changes in the electrocardiogram following the administration of strophanthin are caused by sensitization of the heart muscle to the acetylcholine liberated by the normal vagal tone.

SUMMARY

1. In normal adults the administration of strophanthin, of acetylcholine, and vagal stimulation cause the same electrocardiographic changes in the same subject, viz., bradycardia, relative shortening of electrical systole, and, when the bradycardia is pronounced, changes in the P-waves in Leads II and III.

2. The fact that the changes in the electrocardiograms following vagal stimulation and the administration of acetylcholine are identical indicates that acetylcholine is the vagus substance.

3. The changes in the electrocardiogram following the administration of strophanthin may be harmonized with the hypothesis that strophanthin sensitizes the heart muscle to acetylcholine.

REFERENCES

1. Abdon, N.-O., and Nielsen, Niels A.: The Localization of the Cardio-Inhibitory Vagal Effect Caused by Digitalis, *Skandinav. Arch. Physiol.* 77: 64, 1937.
2. Abdon, N.-O., and Nielsen, Niels A.: On the Mechanism of the Chronotropic Digitalis Effect, *Skandinav. Arch. Physiol.* 77: 65, 1937.
3. Gremels, H.: Über den Einfluss von Digitalisglykosiden auf die energetischen Vorgänge am Säugetierherzen, *Arch. Exper. Path. u. Pharmacol.* 186: 625, 1937.
4. Larsen, K. H., Neukirch, F., and Nielsen, Niels A.: Electrocardiographie Changes in Normal Adults Following Digitalis Administration, *AM. HEART J.* 13: 163, 1937.
5. Routier, C., and Puddu, V.: Étude clinique de l'action de la digitale sur l'électrocardiogramme, *Arch. d. mal. du coeur* 28: 800, 1935.
6. Cohn, A. E., and Levy, R. L.: A Comparison of the Action in Patients of g-Strophanthin and Digitalis, *Proc. Soc. Exper. Biol. & Med.* 17: 81, 1920.
7. Kahlson, G.: Beitrag zur Diagnose der Herzmuskelschwäche, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* 40: 421, 1928.
8. Aschenbrenner, R.: Über das Digitalis-Elektrokardiogramm, *Klin. Wchnschr.* 15: 1039, 1936.
9. Carmichael, E. A., and Fraser, F. R.: The Effects of Acetyl Choline in Man, *Heart* 16: 263, 1933.
10. Weiss, S., and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease, *Medicine* 12: 297, 1933.
11. Nathanson, M. H.: Effect of Drugs on Cardiac Standstill Induced by Pressure on the Carotid Sinus, *Arch. Int. Med.* 51: 387, 1933.
12. Selenin, W. P.: Das Elektrokardiogramm und die pharmakologischen Mittel aus der Gruppe des Gitalins und des Digitoxins, *Arch. f. d. ges. Physiol.* 143: 137, 1912.
13. Bickel, A., and Pawlow, M.: Über den Einfluss einiger Herzmittel auf die Kurve des Elektrokardiogramms, *Biochem. Ztschr.* 48: 459, 1913.
14. Cohn, A. E., and Stewart, H. J.: The Relation Between Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Normal Dogs, *J. clin. Investigation* 6: 53, 1928.
15. Bams, W. A.: The Effect of Digitalis on the Electrocardiogram, *Arch. Int. Med.* 43: 676, 1929.
16. Goldenberg, M., and Rothberger, C. J.: Über die Wirkung von Acetylcholin auf das Warmblüterherz, *Ztschr. f. d. ges. exper. Med.* 94: 151, 1934.
17. Einthoven, W.: Weiteres über das Elektrokardiogramm, *Arch. f. d. ges. Physiol.* 122: 517, 1908.
18. Hering, H. E.: Experimentelle Studien an Säugethieren über das Elektrokardiogramm, *Arch. f. d. ges. Physiol.* 127: 155, 1909.
19. Rothberger, J., and Winterberg, H.: Über die Beziehungen der Herznerven zur Form des Elektrokardiogramms, *Arch. f. d. ges. Physiol.* 135: 506, 1910.
20. Kisch, B., and Sakai, S.: Die Änderung der Funktion der extrakardialen Herznerven durch Änderung der Blutzirkulation, *Arch. f. d. ges. Physiol.* 198: 86, 1923.

VARIATIONS IN A-V AND V-A CONDUCTION DEPENDENT
UPON THE TIME RELATIONS OF AURICULAR
AND VENTRICULAR SYSTOLE: THE
SUPERNORMAL PHASE

EDWARD M. KLINE, M.D., JEROME W. CONN, M.D., AND
FRANCIS F. ROSENBAUM, M.D.
ANN ARBOR, MICH.

IN 1912, Adrian and Lucas¹ designated as the "supernormal phase" a biological phenomenon which they demonstrated in injured excitable tissue. They found that there was a short period during recovery from a previous stimulus in which the tissue became hypersensitive to new stimuli. They showed, further, that this supernormal excitability of nervous tissue was accompanied by a supernormal variation in conductivity. For example, it was shown that an impulse which was ordinarily unable to traverse a depressed zone in a nerve was conducted if it followed a transmitted impulse by an interval of 0.015 to 0.1 second. Adrian² pointed out later that an acid medium was necessary for the existence of the supernormal phase.

Ashman³ produced varying degrees of A-V block in the turtle heart and observed the existence of a supernormal phase in some of the specimens that had been handled repeatedly. He produced an A-V block which was just complete for impulses arriving every fifteen to twenty seconds. When, however, an auricular impulse was sent in about three or four seconds after one of the regularly blocked impulses, it was transmitted. In other words, when an impulse was timed to fall in the supernormal phase of the preceding blocked impulse, it traversed a block through which it could not pass at any other time. Ashman showed, too, that if one impulse passed the block, the following impulses could also be transmitted providing that each impulse occurred during the supernormal phase of the preceding beat.

The existence of a supernormal phase in the human heart was first suggested by Lewis and Master.⁴ In their first case, one of complete heart block, A-V transmission occurred whenever the P-wave fell between the summit and the end of the T-wave of the preceding idioventricular systole. This zone, which they likened to the supernormal phase of Adrian and Lucas, was found to lie between the limits of 0.425 and 0.708 second after the initial movement of the QRS complex. In their second case, one of partial heart block with dropped beats, the zone of effective auricular impulses could not be so sharply defined.

From the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor. This study was assisted by a grant to Frank N. Wilson from the Horace H. Rackham School of Graduate Studies.

Received for publication Sept. 19, 1938.

Wilson and Herrmann⁵ reported a case of paroxysmal complete heart block which is strikingly similar to the first case described in this article. The data pertaining to this case were re-examined and again reported by Ashman and Herrmann,⁶ who found that periods of complete heart block were preceded by periods of gradual auricular slowing. When the length of the cardiac cycle measured from 0.90 to 1.10 seconds, a period of complete heart block followed. Such periods of block were usually interrupted when an auricular systole followed an idioventricular beat by 0.31 to 0.795 second. A critical zone during which the conducting mechanism was reactive to an auricular impulse was therefore present.

Wolferth⁷ reported a case of complete heart block with occasional ventricular responses. He found that when auricular systole occurred 0.45 to 0.74 second after the beginning of the preceding QRS complex, the impulse was transmitted. Wolferth stated that although a supernormal recovery phase could explain the occasional transmitted beat, he preferred to attribute it to an improved nutritional state of the depressed zone during that short period of the cardiac cycle. His chief reason for rejecting the concept of the supernormal phase was the fact that at the time of his report no good evidence existed that a supernormal phase occurred in the mammalian heart.

The purpose of this report is to demonstrate in two cases of heart block the existence of a supernormal phase in conductivity. In the first case an impulse arising in the ventricle frequently established in the depressed zone a supernormal phase during which an auricular impulse passed. This successful A-V conduction produced another supernormal phase during which the next auricular impulse was transmitted. In the second case, impulses arising in the auricle produced in the depressed zone a supernormal phase permitting retrograde conduction.

CASE 1.—E. P., a 45-year-old, white male laborer, was admitted to the University Hospital Sept. 21, 1937, complaining of fainting spells. He stated that he had enjoyed good health until six months before admission, when he experienced his first attack of syncope. Attacks had become more frequent so that they occurred almost daily. During attacks he had noticed some irregularity of the heart which he described as "missed beats." There was no history of rheumatic fever or syphilis.

On physical examination, the patient was a well-developed adult male who did not appear severely ill. On several occasions during the examination there occurred transient pronounced pallor of the face, accompanied by a staring facial expression and momentary disorientation. During these attacks, which lasted only a few seconds, the patient was pulseless. In similar but more severe attacks, syncope occurred and ventricular asystole lasted as long as five seconds. Recovery was characterized by intense flushing of the face and the return of normal cardiac rhythm. Except for the cardiovascular findings to be described, the physical examination revealed no abnormalities. The pulse was small and sustained. The blood pressure in the left arm was 138/110, and in the right arm 108/92. The heart was not enlarged on percussion. A loud, rough systolic murmur, transmitted to the vessels of the neck, was heard at the aortic area, where a systolic thrill could be felt. Along the left border of the sternum in the third intercostal space a soft, blowing, high-pitched, diastolic murmur was heard. Both aortic stenosis and aortic insufficiency

were thought to be present. At times, when the beating was irregular, auricular sounds could be heard to the left of the sternum (Fig. 4*A*). There were no signs suggesting congestive cardiac failure.

The urine, blood, and stool were normal. The blood Kahn reaction for syphilis was negative. An orthodiagram revealed definite cardiac enlargement; the frontal plane area was 38 per cent and the total transverse diameter 25 per cent above the average for normal subjects of the patient's height and weight. No calcification of the aortic valve could be made out. Roentgenologic examinations of the spine, soft tissues of the neck, and upper gastrointestinal tract demonstrated no abnormalities.

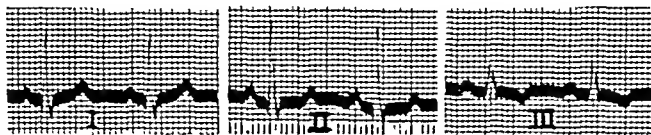


Fig. 1.—Case 1. Sept. 21, 1937. Day of admission. No spontaneous attacks. Carotid sinus pressure not applied.

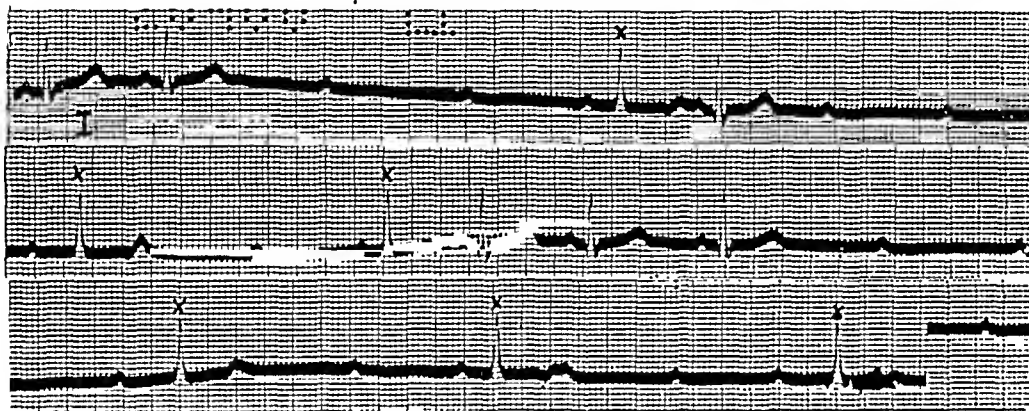


Fig. 2.—Case 1. Sept. 22, 1937. Lead I taken during spontaneous attacks of syncope. Idioventricular beats marked X. Continuous tracing.

The first electrocardiogram, taken when the patient was having no spontaneous attacks, was normal (Fig. 1). The heart rate was 83 per minute and the P-R interval 0.18 second. On the following day there were frequent spontaneous Adams-Stokes attacks. These were relieved by the hypodermic injection of 0.5 c.c. of adrenalin hydrochloride (1:1000 dilution). The electrocardiogram (Fig. 2) taken during these seizures showed repeated intervals of complete heart block associated with ventricular standstill or very slow idioventricular rhythm. The periods of complete heart block were separated by short intervals of normal rhythm. Similar episodes of complete heart block could be induced by carotid sinus pressure. Electrocardiograms were taken to demonstrate the effect of carotid sinus stimulation before (Fig. 3*A*) and after (Fig. 3*B*) the injection of 0.5 c.c. of adrenalin hydrochloride. These indicate that the drug prevented prolonged ventricular standstill by inducing the prompt onset of idioventricular beats.*

Figure 4*A* is a record taken 30 minutes after the hypodermic injection of 0.0012 gm. of atropine sulfate. There is no essential difference between this curve and those showing intermittent heart block. Twenty minutes after a second, similar

*From the examination of Fig. 3*B* it may not be at once apparent that complete A-V dissociation is present. The presence of idioventricular beats is indicated by variations in the form of the QRS deflections. These beats are represented by the ventricular complexes which show the larger R-waves and smaller S-waves.



Fig. 3.—Case 1. Sept. 23, 1937. Lead II. *A*, before adrenalin; *B*, after adrenalin. Note the long ventricular asystole after carotid stimulation, in *A*. The heavy vertical line in *B* represents left carotid pressure. Idioventricular beats marked *X*. *A*₁ and *A*₂ continuous. *B*₁ and *B*₂ continuous.

dose of atropine sulfate, however, the ventricles (Fig. 4*B*) responded normally to the auricular impulses. At this time the normal rhythm could not be disturbed by carotid sinus stimulation (Fig. 4*C*).

Ephedrine sulfate in doses of 0.025 gm. four to six times daily for a period of six days failed to cause any change in the cardiac mechanism or in the frequency

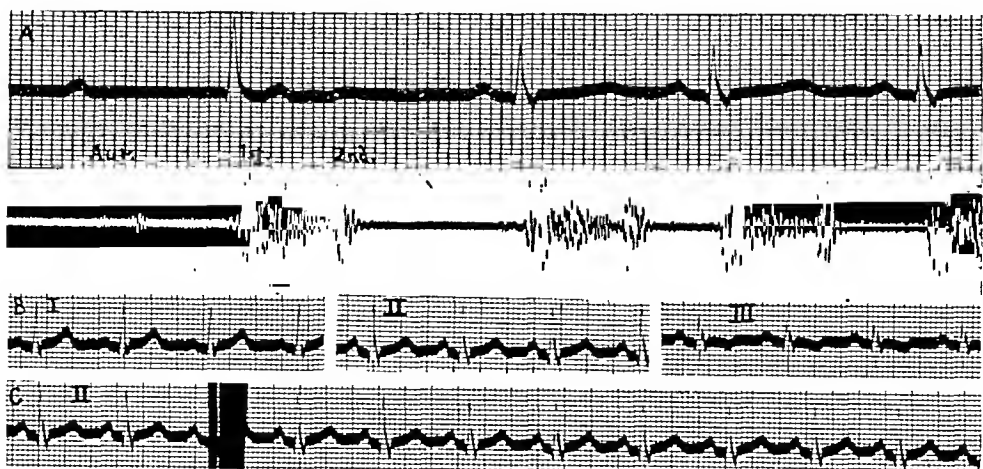


Fig. 4.—Case 1. Sept. 24, 1937. *A*, thirty minutes after atropine sulfate subcutaneously. Note the double auricular sound and the coarse murmur throughout systole. Microphone placed in the third intercostal space, left of sternum. Idioventricular beat in *A*. *B*, twenty minutes after second dose of atropine sulfate. Normal rhythm undisturbed by carotid sinus stimulation in *C*. Heavy vertical line in *C* represents left carotid pressure.

of the periods of asystole. Atropine sulfate by mouth in doses of 0.0004 gm. three to four times daily for a period of five days was also without demonstrable effect.

On Oct. 13, 1937, twenty-three days after the patient entered the hospital, the electrocardiogram showed for the first time partial heart block with three to one response and ventricular escape after each dropped beat (Fig. 5). Except for a brief period of one to one response which resulted from carotid sinus stimulation on Oct. 25, 1937, partial heart block persisted throughout the remainder of the period of hospitalization. With this change in the cardiac mechanism the syncopal attacks disappeared despite increased exercise and frequent carotid sinus stimulation. The patient was discharged from the hospital Oct. 27, 1937. At a check-up examination on April 4, 1938, he stated that he had been working and had had no attacks since leaving the hospital. At this time the electrocardiogram showed complete heart block with abnormal ventricular complexes.

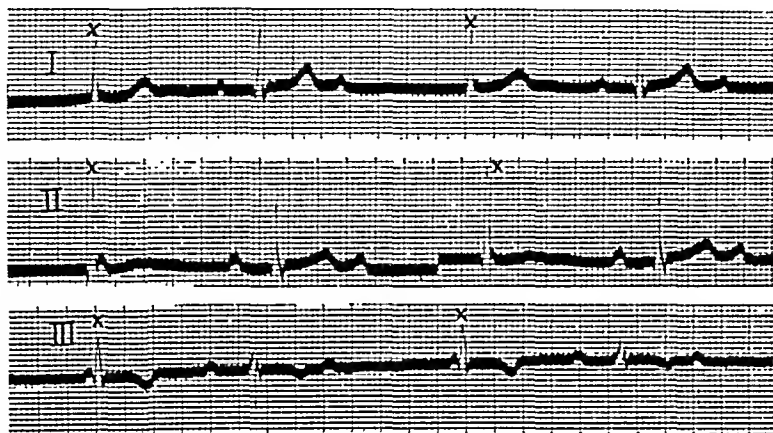


Fig. 5.—Case 1. Oct. 13, 1937. Partial heart block with ventricular escape. Similar to all records obtained during the remainder of hospital course. Idioventricular beats marked X.

Examination of those electrocardiograms showing complete heart block demonstrates several constant relationships. First, complete heart block interrupted the normal rhythm only when there was auricular slowing (Figs. 2, 3A, 3B), regardless of whether this occurred spontaneously or as the result of carotid sinus stimulation. Secondly, normal rhythm was never re-established unless the first transmitted auricular impulse was preceded by an idioventricular beat (Figs. 2, 3, 4). Since not all idioventricular beats were followed by a resumption of one to one response, we compared the time relations of those beats which were followed by resumption of normal rhythm with those which were not.

In order to study these phenomena, two types of measurements were made. All P-P intervals were measured and placed in two groups. In one group were those which were followed by a conducted auricular impulse and in the second were those which were not. Measurements from the initial deflection of the QRS complex of each idioventricular beat to the following P-wave were treated in a similar manner.

From the first set of figures a chart (Chart I) was constructed after the method of Lewis and Master.⁴ This chart shows clearly that the transmitted auricular impulses fall within a definite zone. The upper

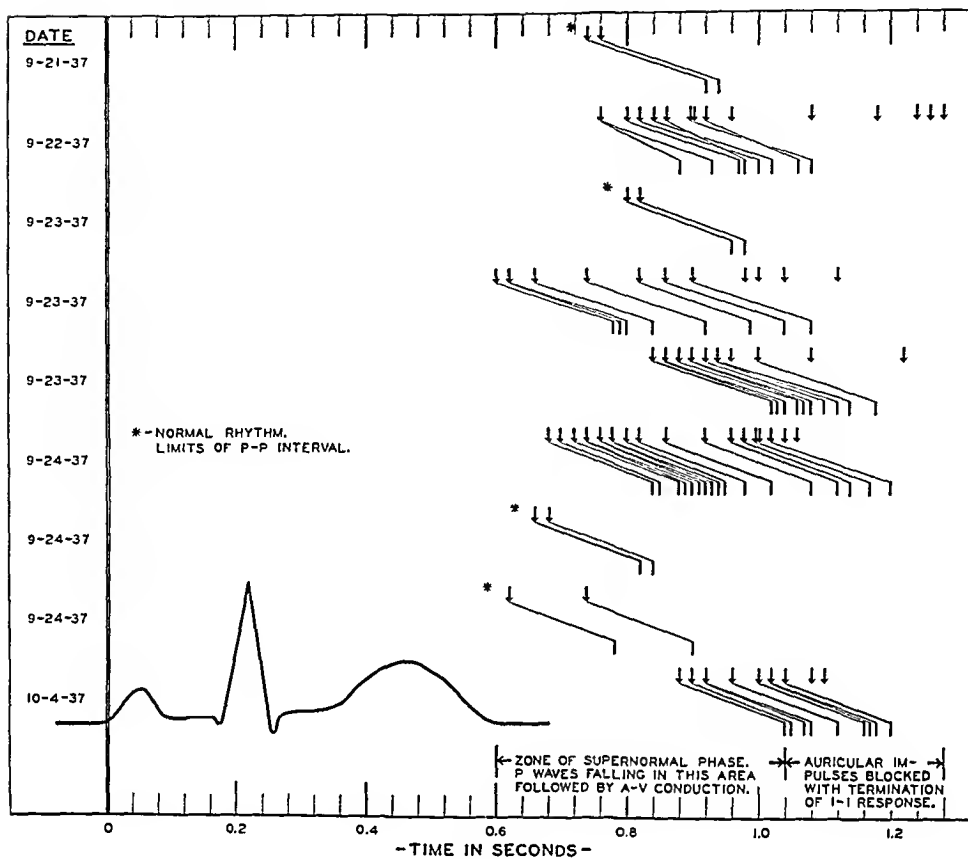


Chart I.

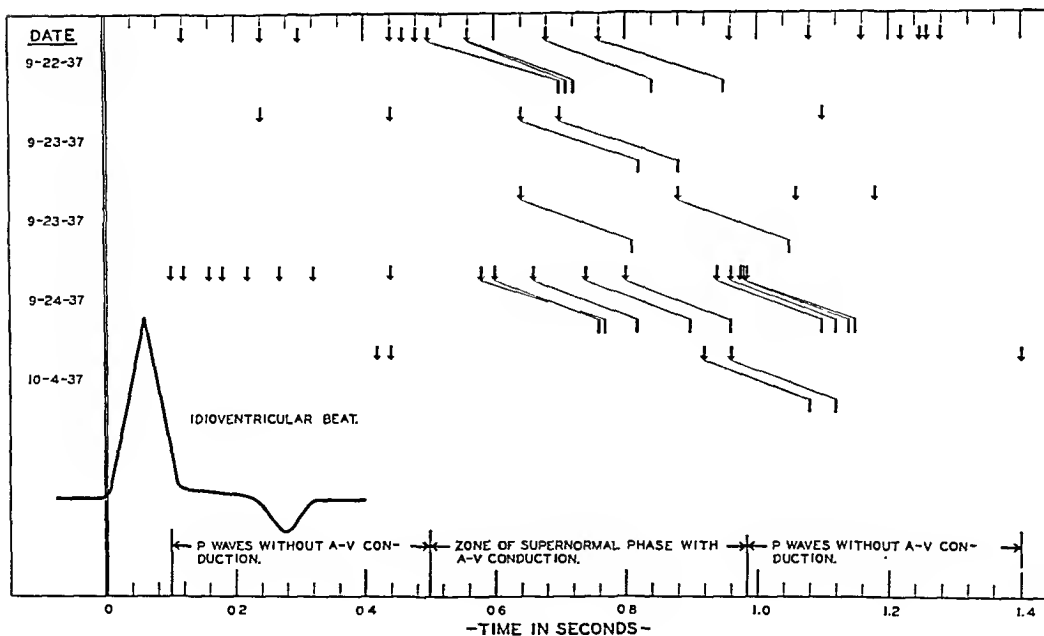


Chart II.

limit of this zone lies between 0.92 second and 1.04 seconds, the lower limit lies at least 0.6 second after the preceding P-wave. No opportunity was afforded to test the lower limit further. Although all of the P-R intervals are within normal limits (varying from 0.12 to 0.19 second) there is no apparent correlation between the length of the P-R interval and the position any particular transmitted impulse occupies within the zone specified. This is in contrast to the findings of Lewis and Master,⁴ who reported in their first case a gradual lengthening of the P-R interval from 0.120 to 0.168 second as the upper limit of the "responsive phase" was reached.

In a similar way it may be demonstrated (Chart II) that there is resumption of one to one response when the P-wave follows an idioventricular beat by an interval of at least 0.50 second. When this interval is 0.90 second transmission frequently fails, and when it is 0.98 second it invariably fails. In as much as failure of A-V conduction is always associated with auricular slowing and is never re-established unless an idioventricular beat occurs, it is clear that fatigue and recovery of the junctional tissues do not explain the observed phenomena.

Although there was apparently a pronounced vagal instability, the variations in vagal tone which occurred are not sufficient to explain the observations made. An increase in vagal tone might explain the onset of the block, but a decrease in vagal tone cannot explain the return of normal conduction. In all instances ventricular standstill was accompanied by auricular acceleration; yet in no instance (this is tested twenty-one times) was there re-establishment of A-V conduction until an idioventricular beat occurred.

We believe, therefore, that a supernormal phase was present during the recovery period of the junctional tissues. The characteristics of the tissue in the region where block occurred were such that the penetration of an impulse into this region from below, or the successful transmission of an impulse from above, was the only circumstance which induced supernormal conductivity. As might be anticipated, the boundaries of the interval during which the depressed region conducted varied slightly from day to day, particularly its upper boundary. Nevertheless, the limits of this interval remained remarkably constant, considering the variety of circumstances under which observations were made.

Chronic complete heart block ultimately occurred, and it is probable that the conduction defect was due to an organic lesion. Since it has been adequately shown that the existence of a supernormal recovery phase is an abnormal phenomenon associated with tissue injury, it is logical to assume that conditions were such as to favor its production in this case. In none of our records in which there was partial block was there evidence that a supernormal phase played a role in determining the cardiac mechanism. Rather, there were indications that recovery and fatigue were acting in the ordinary way; in one instance, when

auricular slowing was produced by carotid sinus pressure, there was continuous, although prolonged, A-V conduction for a short period (Fig. 6).

A review of the electrocardiograms published by Cheer and T'Ang,⁸ and Sachs and Traynor,⁹ which show paroxysmal complete heart block, suggests that the peculiarities of conduction which they observed might also be explained by assuming the occurrence of a supernormal phase during the recovery period of the junctional tissues.

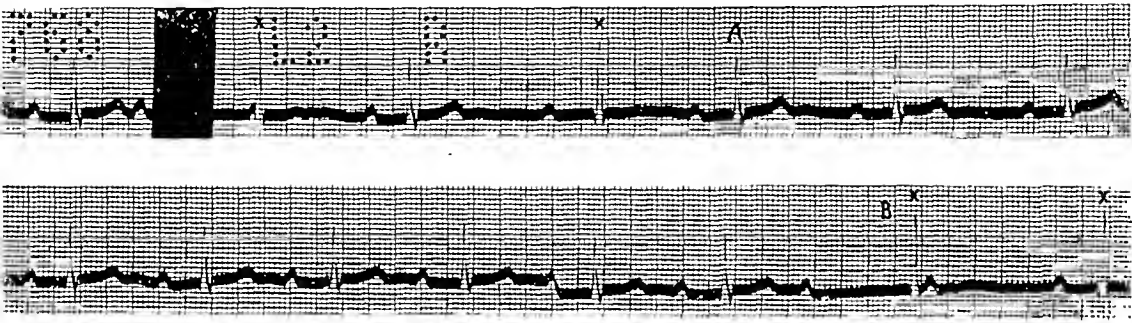


Fig. 6.—Case 1. Oct. 25, 1937. Beginning at A and terminating at B are eighteen responses of the ventricle to the slowed auricle. Result of right carotid pressure. Heavy vertical line represents right carotid pressure. Idioventricular beats marked X. Record is not continuous.

CASE 2.—O. S., a 68-year-old white woman, was admitted to the University Hospital for the first time on Sept. 8, 1933. She then complained of intermittent vaginal bleeding which had been present for two years. There were no symptoms referable to the cardiovascular system.

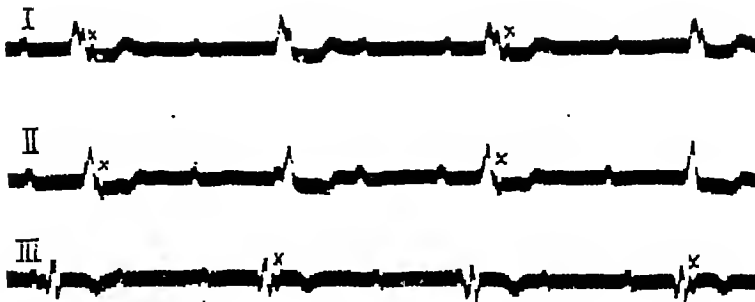


Fig. 7.—Case 2. Dec. 8, 1933. Complete heart block with abnormal ventricular complexes. Ventricular rate 35 per minute. QRS interval 0.14 second. Premature P-waves marked X in all leads, inverted in II and III. QRS-P interval 0.12 to 0.14 second.

On physical examination the patient was very obese. The heart was not enlarged. The heart rate was approximately 84 per minute and the beating was regular. There were no murmurs. The blood pressure was 200/118. A few râles were heard at the bases of the lungs, but there were no other signs suggestive of cardiac failure. Pelvic examination revealed adenocarcinoma of the cervix, a diagnosis proved by biopsy. Radium and deep roentgenotherapy were employed with good immediate result and there has been no recurrence of the tumor.

After leaving the hospital the patient began to notice edema and severe dyspnea. When re-examined on December 7, 1933, the blood pressure was essentially unchanged, but the heart rate was only 37 per minute. The beating was regular. All of the signs of moderate congestive cardiac failure were present. The presence of complete heart block was confirmed by an electrocardiogram (Fig. 7) taken Dec. 8, 1933. The ventricular complexes of this record are strikingly abnormal, and the QRS interval measures 0.14 second. In addition, some of the ventricular complexes are deformed by premature P deflections which are inverted in Leads II and III.

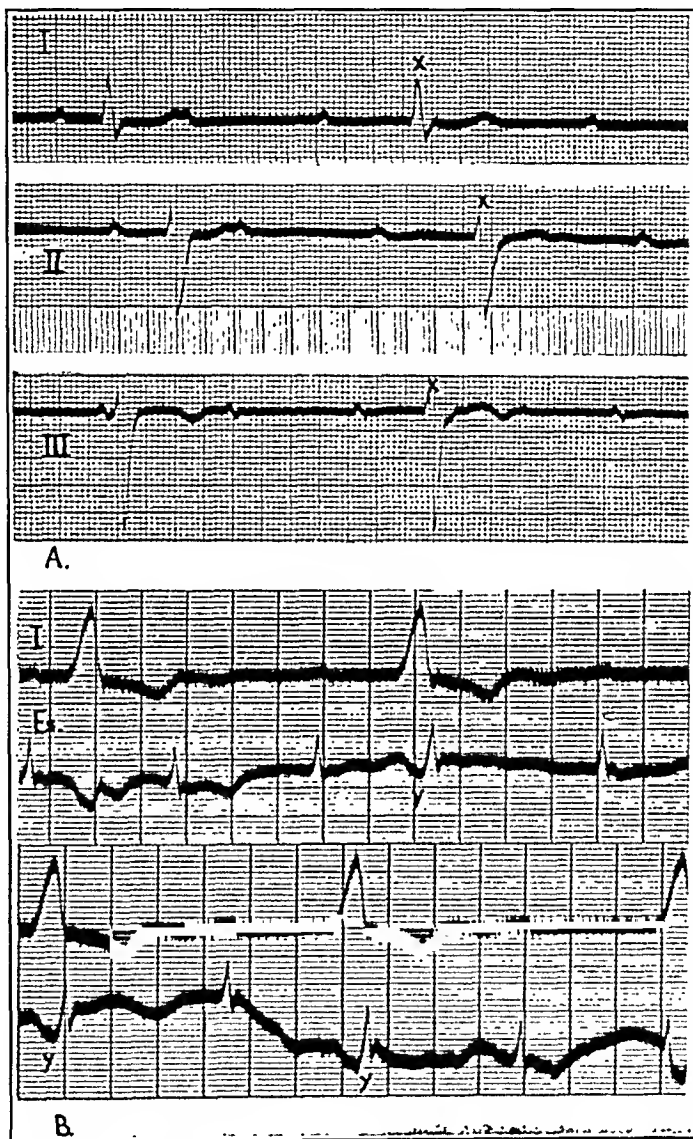


Fig. 8.—Case 2. Dec. 6, 1937. A. Complete heart block with abnormal ventricular complexes. Note in all leads slight deformation of the terminal part of the QRS complexes marked X; interpreted as abnormal P-waves. B. Esophageal lead. Frequent premature auricular contractions following ventricular beats marked Y. R-P interval measures 0.115 to 0.135 second. Record continuous.

A few days after the patient was admitted to the ward auricular fibrillation developed. The ventricular beating became irregular, indicating that the ventricles were responding to the fibrillating auricles. The ventricular rate was relatively slow and after the longer pauses ventricular escape frequently occurred. The ventricular complexes of the idioventricular beats were of the same form as those recorded previously, but the ventricular complexes of the sequential beats were of a

more normal type. They displayed pronounced left axis deviation, but the QRS interval was about 0.11 second. Deflections of this kind suggest the presence of incomplete left bundle branch block. Digitalis had been given just prior to these developments and when it was discontinued the auricular fibrillation disappeared and normal sinus rhythm returned. There was no further change in the contour of the ventricular complexes.

It was not until four years later that the patient was again examined. At this time complete A-V block was again present. In Lead III (Fig. 8A) occasional differences in the termination of the S-wave near the isoelectric line (Fig. 8A, marked X) suggest the occurrence of premature inverted P-waves similar in origin to those recorded in the tracings taken four years earlier (Fig. 7). In order to demonstrate auricular deflections to better advantage, esophageal leads were taken. The most satisfactory for our purpose is that taken with the esophageal electrode 35 cm. from the patient's lips (Fig. 8B).

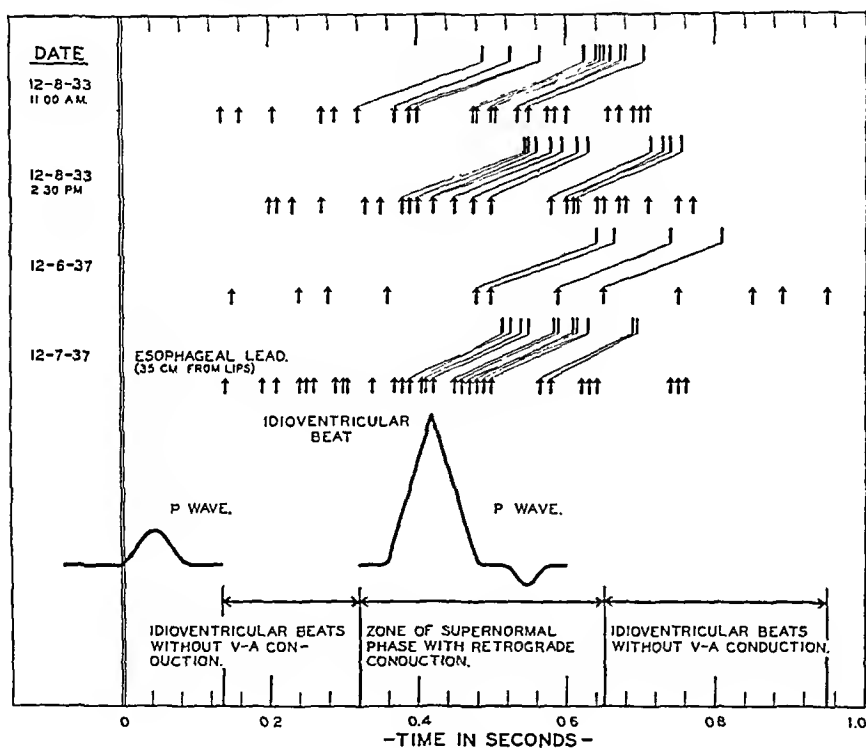


Chart III.

Measurements made from the beginning of each QRS complex deformed by a premature P-wave to the preceding P deflection show that these deformed complexes fall during a well-defined interval. Over the four-year period of observation the limits of this interval are fairly constant. Its extreme limits extend from 0.32 second to 0.65 second after the preceding P-wave.

If we assume that the premature P-waves represent retrograde conduction, an explanation based on the concept of the supernormal phase is suggested. In this instance the supernormal phase is produced by the penetration of the auricular impulse into the region of depressed

conductivity and permits retrograde conduction. A chart (Chart III) illustrating this mechanism has been constructed after the same plan as that used for Case 1.

Cases of a similar kind have frequently been reported in the literature. Some writers (Cohn and Fraser,¹⁰ Wilson and Robinson,¹¹ and Barker¹²) have considered the abnormal premature P-waves to be the result of impulses arising in the lower auricular or upper junctional tissue. Others (Danielopolu and Danulesco,¹³ and Wolferth and McMillan¹⁴) believed that they were due to the occasional retrograde transmission of one of the idioventricular impulses. In these cases it is possible that supernormal conductivity was present, although the examination of the published tracings does not prove this conclusively.

DISCUSSION

Supernormal conductivity in Case 1 was produced by penetration of a ventricular impulse into the depressed region and by successful A-V transmission through it. It is of interest to point out that during the periods of asystole there was always auricular acceleration until the P-P intervals were within the boundaries of the supernormal phase as outlined in Chart I. However, there was never resumption of A-V transmission until an idioventricular beat occurred. This indicates that auricular impulses were ineffective in modifying the conducting properties of the blocked zone unless they passed completely through it. On the other hand, the idioventricular impulses were able to set up a supernormal phase in spite of the fact that they never passed the region of block.

An opposite situation was present in Case 2. Here auricular impulses which presumably penetrated but did not pass the depressed region were effective in producing supernormal conductivity. In view of what has been said regarding Case 1 it is logical to expect that successful V-A transmission would also produce a supernormal phase. If such were the case, A-V transmission should have been resumed if the following P-wave fell within the supernormal phase produced by the retrograde impulse. Since each retrograde impulse was followed by a compensatory pause before discharge of the next auricular systole, this systole was always too late to reach the depressed region during the supernormal period.

Why a supernormal phase in atrioventricular conductivity should lead in one case to improved A-V conduction and in another case to improved V-A conduction is not altogether clear.

SUMMARY

Two cases of transient complete heart block are reported in which there was a supernormal phase in the conductivity of the depressed region. In the first case, penetration of the depressed zone by an impulse arising in the ventricle produced a supernormal phase during

which A-V conduction occurred. The conducted impulse in turn gave rise to a supernormal phase which permitted the next impulse to pass, so that normal sinus rhythm was established. It was maintained until auricular slowing caused the auricular impulse to fall outside of the period of supernormal conductivity. In the second case, impulses arising in the auricle produced in the depressed zone a supernormal phase which permitted retrograde conduction.

The authors wish to acknowledge their appreciation of the valuable suggestions and assistance of Dr. Frank N. Wilson and Dr. Franklin D. Johnston in this study.

REFERENCES

1. Adrian, E. D., and Lucas, K.: On the Summation of Propagated Disturbances in Nerve and Muscle, *J. Physiol.* 44: 68, 1912.
2. Adrian, E. D.: Recovery Process of Excitable Tissues, *J. Physiol.* 54: 1, 1920.
3. Ashman, R.: Conductivity in Compressed Cardiac Muscle: II. Supernormal Phase in Conductivity in Compressed Auricular Muscle of the Turtle Heart, *J. Physiol.* 74: 140, 1925.
4. Lewis, T., and Master, A. M.: Supernormal Recovery Phase, Illustrated by Two Clinical Cases of Heart Block, *Heart* 11: 371, 1924.
5. Wilson, F. N., and Herrmann, G. R.: Some Unusual Disturbances of the Mechanism of the Heart Beat, *Arch. Int. Med.* 31: 923, 1923.
6. Ashman, R., and Herrmann, G. R.: Supernormal Phase in Conduction and a Recovery Curve for the Human Junctional Tissues, *AM. HEART J.* 1: 594, 1926.
7. Wolferth, C. C.: So-called Supernormal Recovery Phase of Conduction in Heart Muscle, *AM. HEART J.* 3: 706, 1928.
8. Cheer, S. N., and T'Ang, T. K.: Transient Complete Heart Block With Adams-Stokes Attacks and Normal Auriculo-Ventricular Conduction Between Attacks, *Chinese M. J.* 46: 1081, 1932.
9. Sachs, A., and Traynor, R. L.: Paroxysmal Complete Auriculo-Ventricular Heart Block, *AM. HEART J.* 9: 267, 1933.
10. Cohn, A. E., and Fraser, F. R.: The Occurrence of Auricular Contractions in a Case of Incomplete and Complete Heart Block Due to Stimuli Received from the Contracting Ventricles, *Heart* 5: 141, 1914.
11. Wilson, F. N., and Robinson, G. C.: I. Two Cases of Complete Heart Block Showing Unusual Features, *Arch. Int. Med.* 21: 166, 1918.
12. Barker, P. S.: The Occurrence of Auricular Beats Due to Stimulation of the Auricles by the Contracting Ventricles During Complete Heart Block, *AM. HEART J.* 1: 349, 1926.
13. Danielopolu, D., and Danulesco, V.: Sur la Conductibilit  Retrograde et sur la Phase Refractaire de l'Oreillette, *Arch. d. mal. du C ur* 15: 365, 1922.
14. Wolferth, C. C., and McMillan, T. M.: Observations on the Mechanism of Relatively Short Intervals in Ventriculoauricular and Auriculo-Ventricular Sequential Beats During High Grade Heart Block, *AM. HEART J.* 4: 521, 1929.

THE MEASUREMENT IN MAN BY A PNEUMOCARDIOGRAPHIC METHOD OF THE EXCESS OF ARTERIAL OUTFLOW FROM THE CHEST OVER VENOUS INFLOW DURING THE HEART CYCLE

H. A. BLAIR, PH.D., AND A. M. WEDD, M.D.
ROCHESTER, N. Y.

THE early literature on the pneumocardiogram has been reviewed by Luciani¹ (1911) and by Klewitz² (1918). The first description of the negative thoracic pulse is attributed to Buisson, in 1861. Mosso, in 1878, using a Marey tambour connected with the nasal cavities, first satisfactorily recorded intrathoracic pressure changes. In 1887, Luciani observed by means of a balloon in the esophagus those variations in thoracic pressure that are due to the heart's action. These and later observations indicate that during systole more blood leaves the thorax than returns, while later in the cardiac cycle the deficit is made up by an excess of venous return over arterial output. However, contrary views have been expressed which assert that arterial movement is immediately compensated by venous, with the result that the blood content of the thorax is practically constant during the cardiac cycle.

Measurements of intrathoracic pressure changes made to determine the excess of outflow from the chest over inflow are usually calibrated by the method of Wiedemann³ (1919), in which a manometer connected with the mouth, nose, or trachea records intrathoracic pressure changes. Comparison of the initial excursion with that which results when a known volume is introduced into the recording system by adding a bottle of air forms the basis of calibration. The validity of the method depends on the constancy of the volume of the thoracic cavity, a condition which is probably never fulfilled.

In the method here presented those movements of the chest wall due to the heart beat are recorded with an ordinary pneumograph* connected with a membrane manometer whose movements, when photographed, give records such as Fig. 1*a*, in which an upward deflection corresponds to a diminution of chest volume. Comparison with the electrocardiogram indicates that the thorax collapses for about one-sixth of the cardiac cycle and expands during the remainder. To determine the extent of collapse, the nose is held and a suitable rubber

From the Departments of Physiology and Medicine, School of Medicine and Dentistry, the University of Rochester, Rochester, N. Y.

Received for publication Oct. 10, 1938.

*This is a closed rubber tube, 37 cm. long and 2 cm. in diameter, distended by a coil spring, made by the Harvard Apparatus Company. The recording tambour is a segment capsule about 2.5 cm. in diameter, covered with sheet rubber 0.15 mm. thick. The membrane can be kept quite tight and still allow ample excursion of the light beam at 1.5 M.

bulb is connected with the mouth by a glass tube. The bulb is then squeezed to force into the lungs its contained air, or alternatively, it may be allowed to expand from the empty state and thus remove air from the lungs. This procedure brings about a shift in the level of the oscillations due to a change in the volume of the thorax which is equal to the volume of air in the bulb. A comparison of the extent of the oscillations of the record with this shift permits direct measurement of the decrease in volume brought about by the net loss of blood from the thorax during the early part of the cardiac cycle.

There appears to be but one important assumption in this method, namely, that the addition to, or the removal from, the thorax of a given volume of blood will affect the chest wall in the same way as the addition or removal of an equal volume of air. This is equivalent to assuming that the lungs remain in continual apposition to the chest wall and to the thoracic organs and vessels, and that a pressure change occurring in one part of the lungs is readily distributed over the whole. This assumption appears valid. It is, of course, also assumed that the pressure within the lungs returns to its original value after the introduction or removal of the calibrating air. This condition seems to be satisfied except occasionally in subjects who cannot hold their breath without small involuntary respiratory movements. It may be checked, however, by registering the pressure in the mouth when air is introduced or removed, and noting whether that pressure, and therefore the pressure in the lungs, returns to normal, which it will do if the glottis be open. Such a record is shown in Fig. 2 and will be described later.

A typical calibration record, using a bulb of 24 c.c. capacity, is illustrated by Fig. 1b. It will be seen that the tracing rises as a result of the removal of air from the thorax by means of the bulb, and that the displayed tracing tends to fall slowly. This is due to a small leak in the system through a short length of thermometer tubing which is introduced so that the light beam will return promptly to the camera when the breath is held. In the original record the base line displacement is 17 mm. and the height of the wave about 25 mm., measured from the point *A* to *B*. Thus the change in the volume of the thorax with the heart beat is $\frac{25}{17} \times 24 = 35$ c.c. Measurement is made from *A* to *B* because the downward wave that just follows the R-wave of the electrocardiogram is due to the apex thrust of the heart. Since this wave varies from a small oscillation in some subjects (e.g. Fig. 1a) to a large wave such as that seen in Fig. 1b in others, it is clear that it should not be included in the volume change attributed to the movement of blood.

As already mentioned, when the pressure in the lungs is recorded simultaneously and is seen to return to its initial level the method is more reliable. Fig. 2 represents such a record; the upper tracing is

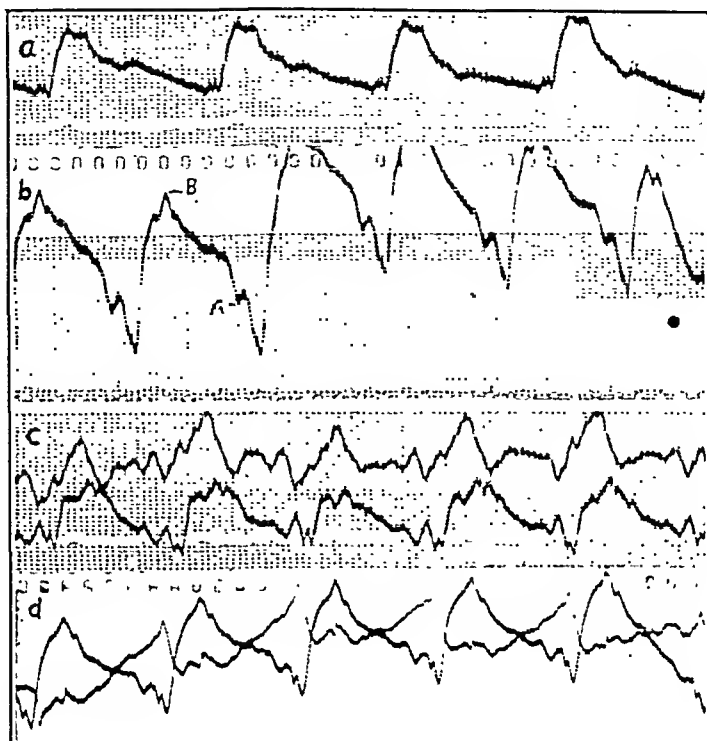


Fig. 1.—*a*, Lead I of the electrocardiogram and a normal pneumocardiogram with the pneumograph just below the sternum. An upward movement is due to collapse of the thorax. *b*, Calibration in another subject. The displacement of the tracing is due to the removal of 24 c.c. of air from the lungs. There is a large apex thrust, shown by the downward movement (expansion of the thorax) occurring just after the R-wave. *c*, Upper record from the mouth with the glottis open, a rise in the tracing denoting a fall in the pressure in the mouth. Lower record, simultaneous pneumocardiogram. *d*, Simultaneous records of the pneumograph on the chest and of the pressure in the mouth with the glottis closed. The tracing from the chest goes lower and that from the mouth gives the left hand peaks of the pairs at the top. All records taken with the subject sitting.

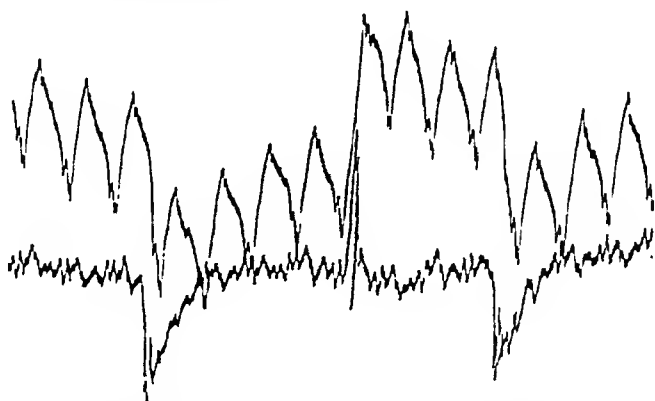


Fig. 2.—Upper tracing, displacement of the pneumocardiogram resulting from the introduction into, or removal from, the thorax of 24 c.c. of air. Lower tracing, the pressure in the mouth and lungs. The large deflections downward in the tracing from the mouth are due to the introduction of 24 c.c. of air into the mouth-lung system. The upward deflection is caused by the removal of 24 c.c. of air. There was a leak in the pneumograph recorder, none in the mouth-pressure recorder.

the pneumogram and the lower is from a manometer connected with the mouth. The first large downward deflection of the tracing from the mouth is due to the introduction of 24 c.c. of air from the bulb; the second large deflection, which is upward, is due to the more rapid removal of 24 c.c., and the third deflection, again downward, to reintro-

ducing 24 c.c. The chest expands or contracts in response to the bulb. There is some drift of the chest tracing because of the leak. It can be seen that the mouth pressure returns to about its initial level in each instance, indicating that the lung pressure does also, since the glottis is open. The evidence for an open glottis is the small oscillation of the mouth tracing, a point which will be discussed later.

By this method of calibration we have measured the excess of arterial outflow over venous inflow during the cardiac cycle in four subjects. For the first, the average of twelve measurements was 26 c.c., the upper and lower limits being 30 c.c. and 23 c.c., respectively. For another subject, four determinations, made on different days, ranged from 26 c.c. to 37 c.c., with an average of 32 c.c. A third subject, on one occasion, gave three values from 25 to 28 c.c., and a fourth, 26 c.c. and 28 c.c. for two estimations. The average value for the four subjects was 28 c.c. Variations are due in part to real variation in output, and in part to inaccuracies in the method. When mouth pressure is recorded simultaneously, the variations are referable largely to the choice of points from which the deflections are measured, and to the effect of the leak, neither of which is likely to amount to more than a few cubic centimeters. In any case, it may be concluded that the excess of output over inflow is of the order of 30 c.c.

These values are much higher than those obtained by the method of Wiedemann.³ For example, Hamilton⁴ (1930) concluded that in man there cannot be more than about 1 c.c. excess of arterial outflow over venous inflow, and that this occurs only during the first sixth of the cardiac cycle. His conclusion necessitates the further one that venous return occurs for the most part only during systole. Likewise, Klewitz and Baumm⁵ (1921) reach a similar conclusion from dog experiments; their figures for excess of outflow range from 0.22 c.c. to 0.48 c.c. It is evident that the very factor on which the present method is based, the movement of the thoracic wall in response to internal pressure changes, is just the one which introduces a large error into the Wiedemann method, for any compensatory movement of the chest wall or diaphragm will diminish the pressure changes in the mouth.

Inasmuch as most observations on the pneumocardiogram, including those reported recently, have been made with oral recording, it is desirable to compare simultaneous tracings from the mouth and chest. In the example Fig. 1c, the upper tracing is from the mouth with the glottis open and the lower is from the chest wall. It will be noted that the tracing from the mouth begins to rise just after the peak of the R-wave, indicating lowering of mouth pressure, and it continues upward as the chest tracing goes downward. This rise is simultaneous with the beginning of the downward movement of the chest record due to the apex beat. The relationship is explained by the fact that the apex beat, which is associated with an outward movement of the chest wall, lowers

the pressure in the lungs, and so the mouth pressure will begin to decline with the apex beat and continue while ejection takes place, whereas in the chest tracing apex beat and ejection give rise to movements which are opposite in direction. It will also be seen that the pressure in the mouth reaches its minimum before the size of the thorax does. This is to be expected, since the mouth pressure will be low only until the chest walls have collapsed sufficiently to restore the lungs to atmospheric pressure. In other words, the tracing from the mouth registers only the lag of the chest wall and the diaphragm in their movements to compensate for pressure changes in the lungs.

Moreover, the influence on the tracing from the mouth of blood going to the tissues of the mouth and throat, as well as that of air pressure changes in the lungs, must be considered. This is illustrated by Fig. 1*d*, which shows simultaneous tracings from the chest and mouth with the glottis closed. Here it is seen that the pressure in the mouth begins to *increase* rather than decrease just before the chest begins to collapse, reaches a maximum, and then declines slowly. Thus, with the glottis open, lowering of the pressure in the mouth secondary to the lowering in the lungs is compensated to some extent by a rise in mouth pressure produced by the pulse in surrounding tissues. The entry of this factor can be seen as a notch on the rise of the tracing made with the glottis open (Fig. 1*c*), but its importance is difficult to estimate because when the glottis is open the volume of air in the recording system is greatly increased by the addition of the lung volume. Some subjects show more sustained lowering of mouth pressure when the glottis is open than in the illustration used, perhaps because of a tendency for the glottis to close when air is taken from the mouth to the lungs.

Attempts to obtain records with both the mouth and the glottis open were made in order to see whether the thoracic movement was appreciably altered when compensation was possible by air movement through the trachea. Without recording, it is difficult to be certain that the glottis is open, but from records taken when the glottis was thought to be open the chest movement was practically unchanged in amplitude, though perhaps slightly in form. It appears easier for internal pressure changes to move the chest wall than to force air through the trachea.

From such considerations it is clear that the tracing from the mouth alone cannot give an accurate measure of the flow of blood to and from the thorax, and that the assumption of negligible compensation by the chest wall and diaphragm is untenable. Indeed, it appears that the flexibility of the thoracic cage and the diaphragm is so great that it introduces into the calibration by the Wiedemann method an error which amounts to approximately 90 per cent. It may be added that the flexibility of the thorax favors arterial rather than venous flow. While normally the aspiratory action is not very important, if the chest were

rigid the outflow from the chest would exert its aspiratory effect almost entirely on the inflow, and then energy would be lost by the arterial system. Reduced flexibility due to rigidity of the lungs must significantly alter cardiodynamics.

SUMMARY

The movements of the chest wall caused by the heart beat were recorded photographically from an ordinary pneumograph during suspended respiration. To calibrate the excess of outflow of blood from the chest over inflow during the early part of the cardiac cycle the oscillations of the record were compared with the displacement obtained by introducing into the thorax, or removing from it, 24 c.c. of air by way of the mouth. It is concluded that the excess of arterial outflow over venous inflow is approximately 30 c.c. Reasons for the low values, about 1 c.c., which have been obtained previously by tracings from the mouth alone are discussed.

REFERENCES

1. Luciani, L.: Human Physiology, Vol. 1. English edition translated by Welby. London, 1911, The Macmillan Company.
2. Klewitz, F.: Die kardiopneumatische Kurve, *Deutsches Arch. f. klin. Med.* 124: 460, 1918.
3. Wiedemann, G.: Zur Bestimmung des Herzschlagvolumens, *Deutsches Arch. f. klin. Med.* 129: 325, 1919.
4. Hamilton, W. F.: Filling of the Normal Human Heart in Relation to the Cardio-Pneumogram and Abdominal Plethysmogram, *Am. J. Physiol.* 91: 712, 1930.
5. Klewitz, F., and Baumm, F.: Über die durch die Herzaktion bedingten intrathorakalen Druckschwankungen und ihre praktische Verwertung, *Deutsches Arch. f. klin. Med.* 135: 108, 1921.

CIRCULATORY EFFECTS OF INTRAVENOUS INJECTION OF FIFTY PER CENT DEXTROSE AND SUCROSE SOLUTIONS IN PATIENTS WITH HEART DISEASE*

LAURENCE B. ELLIS, M.D., AND JAMES M. FAULKNER, M.D.
BOSTON, MASS.

IN THE practice of clinical medicine and surgery the intravenous administration of 50 per cent dextrose solution is a therapeutic measure commonly employed in a variety of conditions and with various ends in view. Its use has been advocated with the object of supplying needed sugar, of raising arterial blood pressure and increasing blood volume, of reducing intracranial tension, and of effecting diuresis. Dextrose is frequently administered to patients with heart disease either with the purpose of benefiting the cardiac condition itself or as therapy for some other condition when the heart disease is incidental.

In spite of the widespread use of this substance and the numerous clinical reports in the literature, there is a paucity of reported experimental studies dealing with its actual effect on the hemodynamics of the circulation in man.

A number of experimental studies on animals have been reported concerning the effect of hypertonic dextrose solution on the minute-volume output of the heart, the blood volume, the arterial blood pressure, and the heart rate. Kisch,¹ using a 4 per cent dextrose solution in physiologic saline, and Mazzola and Torrey,² employing a 50 per cent solution, found that in the cat there was an increase in cardiac output persisting from 30 minutes to two hours. Onozaki³ found that the injection of 25 per cent dextrose solution produced the same effect in the rabbit. Hamm and Pileher⁴ reported that one and two hours after a large injection (100 c.c. per kilogram body weight) of 50 per cent dextrose solution in dogs the cardiac output was usually somewhat reduced. Several studies^{5, 6, 7} have been made in animals indicating that the plasma volume is increased immediately following the injection of hypertonic dextrose solution. Most investigators agree that when hypertonic solutions of dextrose are administered experimentally to animals in quantities proportionally greater than were used in the present study there is a moderate increase in blood pressure after an initial drop, the rise persisting for one to two hours. Unless very large amounts of solution are given the heart rate shows no change, or even decreases.

*Read by title before the American Society for Clinical Investigation, Atlantic City, N. J., May 2, 1938.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

Received for publication Oct. 17, 1938.

In man the reported work on the effect on the circulation of injecting hypertonic dextrose solutions is very meager. Gibson and Evans⁸ found that following the intravenous injection of 50 c.c. of 50 per cent dextrose solution into a normal subject there occurred within five minutes an increase in blood volume of about 200 c.c. Massermann⁹ noted no change in arterial blood pressure or heart rate during or following the injection of large amounts (up to 200 gm.) of hypertonic dextrose solution, although Yesko, Passalacqua, and Judd¹⁰ found a transitory increase in systolic blood pressure and heart rate and a decrease in diastolic pressure after the injection of about 1000 c.c. of 1 per cent salt solution containing 10 per cent dextrose.

Certain reported studies concerning the hemodynamic effects of the injection of comparatively large amounts (500 to 1500 c.c.) of isotonic or mildly hypertonic (5 per cent dextrose in normal saline) solutions are pertinent to our study. In the papers of Gilligan, Altschule, and Volk¹¹ and Altschule and Gilligan¹² it was shown that in persons with normal cardiovascular systems there was an increase in plasma and blood volumes immediately following the injection. The magnitude of this increase was dependent on the rate of injection and might persist for two hours. If the rate of injection exceeded 20 c.c. per minute, considerable increases in venous pressure, cardiac output, and velocity of blood flow, and occasionally in pulse rate and pulse pressure, occurred during the injection. The increase in venous pressure never lasted more than ten to twenty-five minutes.

Caughey¹³ and Richards, Caughey, et al.,¹⁴ could demonstrate very little change in venous pressure when 1500 to 2500 c.c. of normal saline were infused into normal individuals at a rate of 50 c.c. per minute, but when cardiac patients were studied a progressive rise in venous pressure occurred.

Recently there have appeared reports advocating the intravenous administration of 50 per cent sucrose solution, rather than dextrose, in certain clinical conditions. Keith, Wakefield, and Power¹⁵ demonstrated that large amounts could be given intravenously to man without toxic effect and that it was excreted quantitatively in the urine within twenty-four hours. Because the sucrose molecule, being larger and less diffusible than dextrose, theoretically should remain in the blood longer, and since it was neither broken down, nor utilized, nor stored in the body, it appeared rational to believe that hypertonic sucrose solutions would be more efficient than dextrose in maintaining blood volume and in causing diuresis, and would not produce the secondary rise in spinal fluid pressure which had been observed following the injection of dextrose. The studies of Bulloek, Gregersen, and Kinney¹⁶ on dogs, and the work of Massermann¹⁷ concerning the effect of sucrose on reducing spinal fluid pressure in man, and that of Murphy, Hershberg, and Katz¹⁸ on its action in relieving intracranial tension in patients with severe

arterial hypertension, as well as certain reports regarding its diuretic effect,^{19, 20} have tended to confirm the theoretical basis for the value of suerose. No work on the effect of this substance on the hemodynamics of the circulation has been reported other than the observation that massive injections (300 to 500 c.c.) of a 50 per cent solution produce little effect on the blood pressure.¹⁸

Although it is generally assumed that the use of either 50 per cent dextrose solution in quantities up to 100 c.c. or of larger amounts of isotonic or mildly hypertonic solutions is a relatively safe procedure, serious reactions have been observed. Clark²¹ has reported two deaths after the administration of 500 c.c. of a 10 per cent solution of dextrose in normal saline, and one following a like amount of normal saline. The question always arises whether the mode of injection, the substance itself, or some extraneous factor is responsible for such an untoward happening.

The present study was undertaken to ascertain what changes actually take place in the circulation of cardiac patients as well as of individuals with normal cardiovascular systems during and following the intravenous injection of 50 per cent dextrose and suerose solutions. From such a study information may be gained regarding the therapeutic effectiveness and possible dangers of this procedure.

METHOD

All procedures were carried out with the patient recumbent following a period of rest long enough to stabilize the arterial blood pressure and the heart rate. The sugar solution was warmed and injected into an antecubital vein at a rate of 10 c.c. a minute. A total of 100 c.c. was given in each instance. Ordinary commercial ampules of dextrose solution were employed. The suerose used was in part a commercial preparation* and in part consisted of several lots made up in the laboratory by dissolving commercial sucrose in freshly distilled water and sterilizing it by passage through a Berkefeld filter.

Once or twice the subject complained of pain at the site of the injection or along the course of the vein. If this occurred the experiment was stopped. Of the subjects receiving dextrose one complained of slight chilliness forty-five minutes following the injection and one had a mild chill after forty-five minutes. There were more reactions following suerose. On two occasions mild chilliness occurred about an hour after the injection and in five instances chills, varying from mild to severe, took place in from one to two hours. These chills bore no relationship to the lot of suerose employed and may well have been caused by the procedure for determining venous pressure, in which it was necessary to infuse saline solution very slowly over a period of about forty-five minutes. Otherwise the patients experienced no subjective sensations during or following the injection. No definite beneficial effect on the patient's clinical state as the result of the administration of the sugar was apparent.

Observations were made of the arterial and venous blood pressures, the heart rate, and relative changes in the plasma volume as estimated by alterations in the plasma protein and hematocrit values. The arterial blood pressure was measured with a mercury manometer by the auscultatory method. The venous pressure was obtained

*We are indebted to Eli Lilly and Company for supplying us with ampules of 50 per cent sucrose solution.

by the direct method of Moritz and von Tabora²²; readings were taken at one- to two-minute intervals throughout the period of injection and usually for about thirty minutes thereafter. For any subsequent determinations the needle was reintroduced. A total of about 50 c.c. of physiologic saline solution was injected while obtaining the venous pressures, an amount insufficient to produce any demonstrable effect on the venous pressure.

Relative changes in plasma volume were estimated by determining the hematocrit and plasma protein values at intervals following the injection of sugar. Since the total protein content of the plasma can be assumed to be unchanged during the period of the experiment, any change in its concentration is a proportional reflection of change in the water content of the plasma resulting from the injection. The plasma proteins were determined by a modification of Howe's method.²³

Changes in hematocrit values similarly reflect changes in the plasma volume, but, because of the possibility that the hypertonic solution may cause some shrinkage in cell volume or that the procedure might conceivably alter the total number of circulating erythrocytes, this determination is probably a much less accurate estimate of change in plasma volume than is the calculation of change in the plasma proteins. The proportional alteration in plasma volume as estimated by hematocrit change was calculated from a slight modification of the formula of Landis, Jonas, Angevine, and Erb²⁴:

$$\text{Percentage change in plasma volume} = \left[100 \frac{C}{C_1} - 100 \right] \times \frac{1}{100 - C}, \text{ where } C \text{ equals}$$

relative cell volume of blood before the injection of sugar, and C_1 equals relative cell volume following injection.

The estimation of changes in plasma volume by plasma protein determinations has been compared by Gilligan, Altschule, and Volk¹¹ with the determination of blood volume by the method of Gibson and Evans⁸ and found to be accurate. A full discussion of this subject is given in the paper of Gilligan, Altschule, and Volk.¹¹

Thirty-six studies were made, nineteen with dextrose and seventeen with sucrose. Two of the subjects to whom dextrose was given had no evidence of cardiovascular disease; the remainder had heart disease. Of these, three were convalescent from congestive failure, and two had suffered coronary thromboses four and six weeks previously but did not have congestive failure. The remainder were suffering from congestive failure varying in degree from mild to very severe. The majority of this group had both right- and left-sided failure and most of them were severely decompensated.

Of those to whom sucrose was given, three had no cardiovascular disease and the remainder had heart disease. Five of these were compensated at the time of the study and the others were suffering from varying degrees of failure.

Of the total group of cardiac patients, the etiology of the heart disease was hypertension or arteriosclerosis in 20; in five it was rheumatic, and in one it was syphilitic. Five patients were given both sucrose and dextrose.

RESULTS

1. *Effect of Clinical Condition on the Response.*—Although there was considerable variation among different individuals in the results obtained, the cardiac patients tended to respond in the same general way as did the control subjects, and the etiology of the heart disease or the degree or type of heart failure did not apparently influence the response obtained. Because of this and because there were too few patients in each category to permit of statistical analysis, the findings on all subjects are tabulated together.

TABLE I

THE EFFECT OF THE INTRAVENOUS INJECTION OF 100 C.C. OF 50 PER CENT DEXTROSE SOLUTION ON THE VENOUS PRESSURES AND THE PLASMA VOLUME IN TWO CONTROL SUBJECTS AND SEVENTEEN PATIENTS WITH HEART DISEASE

CASE	AGE	DIAGNOSIS	PULMO- NARY CONGES- TION	PERIPE- RAL EDEMA	VENOUS PRESSURE (CM. H ₂ O)					PERCENTAGE CHANGE IN PLASMA VOLUME FOLLOWING COMPLETION OF INJECTION *					
					CON- TROL LEVEL	AFTER INJECTION				1 MIN.	7-10 MIN.	15 MIN.	30 MIN.	60 MIN.	90 MIN.
						1 MIN.	10 MIN.	30 MIN.	60 MIN.						
1	32	Control	0	0	6.0	12.0	7.5	6.0	2.5	+9 (+12)	+11 (+13)	+11 (+6)	+10 (+7)	+3 (-2)	
2	43	Control	0	0	6.5	7.0	7.5	7.0	2.5				(+2)	(+4)	
3	67	Cor. throm.	0	0	5.0	7.0	8.0	8.0	4.5				+5 (-1)	0 (-2)	
4	63	Cor. throm.	+	0	8.0	6.5	3.0	2.0	2.0						
5	52	R. H. D.	0	0	6.5	11.0	8.0	6.5	2.0	+17 (+12)	+6 (+10)		+5 (-3)	-1	+2 (0)
6	49	R. H. D.	0	0	4.0	5.5	6.0	6.5	4.0				+3 (+1)	+4 (+3)	
7	74	Art. scler.	0	0	4.0	4.5	4.0	3.5	3.0				+11 (+7)		
8	76	Art. scler.	+	0	0.5	5.0	3.0	1.0	1.0				(+9)		(0)
9	54	Art. scler.	+	0	1.0	3.0	2.0	3.5	-1.0				+13 (+13)	-8 (-3)	(0)
10	81	Art. scler.	+	+	10.0	17.0	11.0	11.0		+15 (+14)	+11 (+16)	+8 (+11)	+11 (+12)	+15 (+14)	
11	75	Art. scler.	0	+	4.0	5.0	4.0				+15 (+13)	+12 (+15)	+12 (+13)	(0)	
12	56	H. H. D. and Art. scler.	0	+	9.0	11.0	8.5	8.0					(+1)	(0)	
13	60	R. H. D. and Art. scler.	+	+	9.0	11.0	9.5	8.5	9.0				+7 (+23)	0 (0)	
14	63	H. H. D. and Art. scler.	+	+	8.0	12.0	10.0	9.0	8.0				(+4)		(-2)
15	44	H. H. D.	+	+	9.5	11.5	9.0	9.0		+8 (+2)	+8 (+3)	+8 (+2)	+1 (+2)		
16	57	H. H. D.	+	+	18.0	21.5	20.0	17.5		+7 (+7)	+7 (+8)	+6 (+10)	+6 (+8)		
17	35	R. H. D.	+	+	12.5	16.0	13.0			+8 (+5)	+7 (+9)		+3 (+2)		
18	50	H. H. D.	+	+	12.5	15.5	14.5	12.5					+6 (+6)		+7 (+6)
19	48	R. H. D.	+	+	14.5	15.0	15.5	13.0	10.0				+13 (+8)		-3 (-5)

Abbreviations: Cor. throm., Coronary thrombosis; R. H. D., rheumatic heart disease; Art. scler., arteriosclerotic heart disease; H. H. D., hypertensive heart disease.

*Figures without parentheses represent percentage changes in plasma volume calculated from plasma protein changes. Figures in parentheses represent percentage changes in plasma volume calculated from hematocrit changes.

TABLE II

THE EFFECT OF THE INTRAVENOUS INJECTION OF 100 C.C. OF 50 PER CENT SUCROSE SOLUTION ON THE VENOUS PRESSURE AND THE PLASMA VOLUME IN THREE CONTROL SUBJECTS AND FOURTEEN PATIENTS WITH HEART DISEASE

CASE	AGE	DIAGNOSIS	PULMO- NARY CONGES- TION	PERIPH- ERAL EDEMA	VENOUS PRESSURE (CM. H ₂ O)					PERCENTAGE CHANGE IN PLASMA VOLUME FOLLOWING COMPLETION OF INJECTION†					
					CON- TROL LEVEL	AFTER INJECTION				1 MIN.	7-10 MIN.	15 MIN.	30 MIN.	60 MIN.	90 MIN.
						1 MIN.	10 MIN.	30 MIN.	60 MIN.						
20	30	Control	0	0	0	2.5	1.5	1.5	1.0				+19 (+15)		-2 (-6)
21	64	Control	0	0	2.0	4.0	3.0	2.0	1.0				(+10)		0
22	17	Control	0	0	8.0	9.0	8.5	8.5	7.0				-3 (-3)		-1 (0)
23	61	II. II. D.	0	0	8.0	8.5	9.0	8.0	8.0				(+4)		
24	50	II. II. D.	0	0	6.0	12.0	8.0	9.0							
25	52	R. H. D.	0	0	5.0	8.0	5.0	5.0							
26	44	*S. II. D.	0	0	1.0	3.0	2.0	-1.0							
27	54	II. II. D.	0	0	7.0	9.5	10.0	9.5	7.0				(+5)		
28	75	Art. scler.	+	+	0.5	2.5	0.5	0.5					+14 (+8)		+8 (+5)
29	76	Art. scler.	+	+	2.0	6.5	2.0						+14 (+3)		+12 (+12)
30	51	II. H. D.	+	+	10.5	15.5	12.5	10.5					+10 (+25)		+3 (+2)
31	69	II. H. D.	+	+	15.0	21.5	17.5						+8 (+3)		
32	56	II. II. D. and Art. scler.	0	+	10.0	13.0	11.0	21.0	20.0				+4 (+1)		-2 (-4)
33	68	Art. scler.	+	+	0.5	4.5	2.0	1.0							
34	50	II. II. D.	+	+	27.0	31.0	28.5	25.0	24.5				+4 (+9)		-10 (-11)
35	44	II. II. D.	+	+	18.5	24.5	20.0	17.0					+11 (+2)		-8 (+8)

*Syphilitic heart disease. For other abbreviations see Table I.

†See footnote, Table I.

2. *Dextrose Versus Sucrose.*—Although one might expect on theoretical grounds that a given dose of sucrose might have a more prolonged action than the same amount of dextrose, this was not apparent in the results. The great individual variation in the responses prevented accurate analysis of the results, but in general the effects produced by dextrose and sucrose were similar. Both sucrose and dextrose were administered to five patients. All of them showed a tendency to react in a similar fashion to both substances.

3. *Arterial Blood Pressure and Heart Rate.*—Very little effect was observed on arterial blood pressure or on the heart rate. In four instances either the systolic or diastolic blood pressure, or both, increased from 10 to 22 mm. Hg for a short time following the injection, and in five cases the pressure fell a like amount. In the remainder there was no essential change.

In seven cases the heart rate increased from 8 to 10 beats per minute, and once the increase was 20 beats. These increases lasted, as a rule, a very few minutes following the cessation of injection. The remaining twenty-nine subjects showed pulse rate changes of less than 8 beats per minute, usually none at all.

4. *Venous Pressure.*—There was a tendency for the venous pressure to increase throughout the injection and to start to drop again immediately on its cessation. In one instance there was a slight drop of venous pressure during the injection; in every other case it increased, the rise varying from 0.5 to 7 cm. of water, with an average of 2.6 cm. for those who received dextrose, and 3.5 cm. for those who received sucrose. There was no correlation between these changes and the presence or absence of heart disease or the extent or type of heart failure, with the initial level of the venous pressure, or with the amount of increase in plasma volume. The venous pressure had usually returned to the control level within ten minutes after the injection. In six instances it remained elevated by 2 cm. or more for thirty minutes, but in all but one of these cases it had reached the control level in one hour. In a few instances it fell below the control level at the end of thirty to sixty minutes. This was probably caused largely by increased mental and physical relaxation on the part of the subject, but may in part have been the result of a decrease in blood volume caused by the diuretic effect of the hypertonic injection.

5. *Plasma Volume.*—The maximum dilution of the blood plasma, as estimated from the changes in the plasma proteins, took place almost always within one minute after the end of the injection. This increase in plasma volume was in most instances maintained for about thirty minutes, but had usually disappeared in from sixty to ninety minutes. In three cases only was any appreciable increase in plasma volume maintained for sixty minutes (15, 12, and 8 per cent, respectively). Of the nine patients in whom plasma volume changes were studied at the end

of one minute, the increase ranged from 3 to 17 per cent, with an average of 13 per cent (equivalent to approximately 400 c.c. of fluid). In twenty-two patients the change in plasma volume at the end of thirty minutes was noted. In two cases it had fallen below the control level (-3 and -8 per cent respectively). In the remaining twenty it was still elevated by from 1 to 19 per cent, with an average of 9.1 per cent. The apparent decrease of plasma volume which occurred ten times at the end of sixty to ninety minutes may have been due partly to the experimental error of the technique (maximum experimental error about 4 per cent), but was probably mainly an actual decrease resulting from diuresis caused by the hypertonic solution.

The figures for changes in plasma volume calculated from the hematocrit readings are much less reliable than those obtained from plasma protein changes. Although the absolute figures often did not agree, there was a gross correlation between the two sets of figures.

DISCUSSION

The results obtained are consonant with what could be predicted on theoretical grounds. When 100 c.c. of 50 per cent dextrose or sucrose solution are infused into the circulation, the hypertonic action of the sugar rapidly draws fluid into the circulation so that the total increase in plasma volume may reach 400 to 600 c.c. As the result of this rapid increase in circulating blood volume there is an initial increase in venous pressure. The vascular reservoir, however, rapidly adapts itself to this change in blood volume, so that the venous pressure promptly falls to the control level. At the same time as the increase in plasma volume is occurring, physiologic mechanisms are coming into play which tend to cause fluid to go out of the blood stream; diuresis is usually initiated and the sugar diffuses into the tissue spaces, drawing fluid with it. As a result of a balance of these antagonistic forces, the quantitative extent of which is unpredictable, the increase in plasma volume may be maintained as long as thirty minutes, although the return toward normal frequently starts more quickly. In any case, an increased plasma volume rarely persists for more than one hour.

Since it has been shown experimentally in heart-lung preparations and in anesthetized animals that an increase in venous pressure causes an immediate increase in cardiac output, and since such increase in cardiac output with increase in venous pressure has been shown to occur in humans following large amounts of isotonic or mildly hypertonic intravenous infusions,¹² it is reasonable to infer that an increase in cardiac output often does take place under the conditions of our study.

These findings have certain practical clinical implications. In the first place, we have objective experimental confirmation in man for the clinical belief that hypertonic dextrose and sucrose solutions are of but

very temporary value when given to increase blood volume. It is probable that in states of vascular collapse the increase in plasma volume may be of even shorter duration than in the subjects whom we studied. The administration of 50 per cent dextrose solution to increase blood volume will, however, continue to have clinical usefulness in emergency conditions when acute but temporary vascular collapse can be tided over, or in more severe shock while waiting for the more effective measure of blood transfusion.

As far as can be judged from these results, there is no essential difference between the action of dextrose and that of sucrose on the hemodynamics of the circulation.

It is also clear that the injection intravenously of 100 c.c. of 50 per cent dextrose or sucrose solution within ten minutes produces a distinct strain on the cardiovascular apparatus. Although the absolute burden is apparently no greater in cardiac patients than in normal persons, such patients have much less reserve for such emergencies. No untoward results were encountered in the present series, but it seems not unlikely that in an occasional case such an extra load on the circulation of a patient whose cardiac status is already in precarious balance may result in serious consequences.

The intravenous injection of 100 c.c. of 50 per cent dextrose solution at a rate of 10 c.c. per minute is roughly equivalent in its immediate effect on the cardiovascular system to the infusion of 500 c.c. of a 5 per cent solution of dextrose in physiologic saline at a rate of about 30 to 40 c.c. per minute, or of 1000 c.c. at a somewhat slower rate. The clinical use of 50 per cent dextrose solution is therefore rational when it is desired to produce the effect of a markedly hypertonic solution or to introduce sugar parenterally into the body without giving much fluid, but it is not rational to give it with the idea that less strain on the circulation is produced than would result from the injection of a liter of 5 per cent dextrose solution. When the latter is given slowly there probably results less of an immediate strain.

SUMMARY AND CONCLUSIONS

1. The cardiovascular effects resulting from the intravenous injection of 100 c.c. of a 50 per cent solution of dextrose or sucrose were studied in five control subjects and thirty-one patients with heart disease who had varying degrees of cardiac failure.

2. Slight or no changes in the arterial blood pressure and heart rate occurred.

3. The venous pressure tended to increase moderately during the injection, but began to return toward normal immediately on its completion. The increase ranged from 0.5 to 7 cm. of water, with an average of 2.6 cm. for those who received dextrose and 3.5 for those who received sucrose.

4. The plasma volume increased from 3 to 17 per cent (average, 13 per cent) within a minute of the completion of the injection. The rise persisted a varying period of time, but usually by thirty minutes the plasma volume had begun to fall again and in most cases had reached or fallen below the control level within an hour.

5. No difference in the response was noted which could be correlated with the presence or absence of heart disease, or the etiology, degree, or type, of heart failure.

6. The responses obtained with dextrose and with sucrose were similar.

7. The clinical implications of this study, regarding the efficacy of dextrose and sucrose in increasing blood volume, and particularly as relating to the strain thrown on the circulation by such injections, especially in patients with heart disease, are discussed.

We are indebted to Miss Sophia Simmons for assistance in carrying out the technical procedures, and to Miss Margaret Adams and her associates for performing the plasma protein determinations.

REFERENCES

1. Kisch, F.: Experimentelles zur Kreislaufwirkung endovenös einverleibter hyper-tonischer Lösungen, *Ztschr. f. d. ges. exper. Med.* 56: 215, 1927.
2. Mazzola, V., and Torrey, M. A.: An Experimental Study of the Effects of In-travenous Injections of Hypertonic Glucose Solution (50 Per Cent) on the Circulation of the Cat, *Am. J. Obst. & Gynec.* 25: 643, 1933.
3. Onozaki, N.: Studien über die Veränderungen der Kreislaufsdynamik bei in-travasalen Flüssigkeitsinfusionen. IV. Veränderungen des Minuten und Schlagvolumens nach intravenösen Infusionen von hyper und hypotonischen Lösungen, *Tohoku J. Exper. Med.* 24: 580, 1934.
4. Hamm, L., and Pilcher, C.: Cerebral Blood Flow. II. The Effect of Intravenous Injections of Hypertonic and Hypotonic Solutions on the Cardiac Output and Blood Pressure, *Arch. Neurol. & Psychiat.* 24: 907, 1930.
5. Lamson, P. D., and Rosenthal, S. M.: The Inadequacy of Our Present Blood Volume Methods, *Am. J. Physiol.* 63: 358, 1923.
6. Smith, H. P.: Intravenous Injections of Fluid and Repeated Blood Volume Determinations, *Bull. Johns Hopkins Hosp.* 37: 177, 1925.
7. Blalock, A., Beard, J. W., and Thuss, C.: Intravenous Injections. A Study of the Effects on the Composition of the Blood of the Injection of Various Fluids Into Dogs With Normal and Low Blood Pressures, *J. Clin. Investiga-tion* 11: 267, 1932.
8. Gibson, J. G., II, and Evans, W. A., Jr.: Clinical Studies of the Blood Volume. I. Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectrophotometer, *J. Clin. Investigation* 16: 301, 1937.
9. Massermann, J. H.: Effects of Intravenous Administration of Hypertonic Solu-tions of Dextrose With Special Reference to the Cerebro-spinal Fluid Pressure, *J. A. M. A.* 102: 2084, 1934.
10. Yesko, S. A., Passalacqua, L. A., and Judd, E. S.: The Effect on the Circula-tion of the Injection of 10 Per Cent Glucose and 1 Per Cent Sodium Chloride Following Operation, *S. Clin. North America* 9: 969, 1929.
11. Gilligan, D. R., Altschule, M. D., and Volk, M. C.: The Effects on the Cardio-vascular System of Fluids Administered Intravenously in Man. I. Studies of the Amount and Duration of Changes in Blood Volume, *J. Clin. Investigation* 17: 7, 1938.
12. Altschule, M. D., and Gilligan, D. R.: The Effects on the Cardiovascular System of Fluids Administered Intravenously in Man, *J. Clin. Investigation* 17: 401, 1938.
13. Canghey, J. L., Jr.: Effect of Rapid Infusion on Venous Pressure: A Test of Cardiac Reserve, *Proc. Soc. Exper. Biol. & Med.* 32: 973, 1935.
14. Richards, D. W., Jr., Canghey, J. L., Jr., Courmand, A., and Chamberlain, F. L.: Intravenous Saline Infusion as a Clinical Test for Right-Heart and Left-Heart Failure, *Tr. A. Am. Physicians* 52: 250, 1937.

15. Keith, N. M., Wakefield, E. G., and Power, M. H.: The Excretion and Utilization of Sucrose When Injected Intravenously in Man, *Am. J. Physiol.* 101: 63, 1932.
16. Bullock, L. T., Gregersen, M. I., and Kinney, R.: The Use of Hypertonic Sucrose Solution Intravenously to Reduce Cerebrospinal Fluid Pressure Without a Secondary Rise, *Am. J. Physiol.* 112: 82, 1935.
17. Massermann, J. H.: Effects of the Intravenous Administration of Hypertonic Solutions of Sucrose With Special Reference to the Cerebrospinal Fluid Pressure, *Bull. Johns Hopkins Hosp.* 57: 12, 1935.
18. Murphy, F. D., Hershberg, R. H., and Katz, A. M.: The Effect of Intravenous Injections of Sucrose Solution (50 Per Cent) on the Cerebrospinal Fluid Pressure, the Blood Pressure and Clinical Course in Cases of Chronic Hypertension, *Am. J. M. Sc.* 192: 510, 1936.
19. Lowenburg, H., and Nemser, S.: Intravenous Injection of Fifty Per Cent Solution of Sucrose in Edema, *Arch. Pediat.* 53: 762, 1936.
20. Strohm, J. G., and Osgood, S. B.: Intravenous Sucrose as a Diuretic, *Northwest Med.* 35: 89, 1936.
21. Clark, J. H.: Acute Cardiac Dilatation. An Ever Present Danger in Intravenous Injections, *J. A. M. A.* 89: 21, 1927.
22. Moritz, F., and Von Tabora, D.: Über eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsches Arch. f. klin. Med.* 98: 475, 1910.
23. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry. Vol. II, Methods, p. 691. Baltimore, 1932, Williams & Wilkins Co.
24. Landis, E. M., Jonas, L., Angevine, M., and Erb, W.: The Passage of Fluid and Protein Through the Human Capillary Wall During Venous Congestion, *J. Clin. Investigation* 11: 717, 1932.

THE TETRALOGY OF FALLOT

TERMINAL SEPSIS WITH CROSSED EMBOLI

RICHARD F. HERNDON, M.D., ALOYSIUS VASS, M.D., AND

JOHN J. DONOVAN, M.D.

SPRINGFIELD, ILL.

THE following case seems worth reporting because of the presence of the typical tetralogy of Fallot in a man 49 years of age, and because crossed or paradoxical emboli occurred during the terminal sepsis.

REPORT OF CASE

An American salesman, 49 years, six months, twenty-two days of age, was seen (by J. J. D.) March 8, 1938, at which time he was complaining of pain in the right lower chest and shortness of breath.

He was born a "blue baby" and grew up a delicate boy who was not expected to live. However, he learned not to hurry and survived two attacks of pneumonia and one of typhoid fever before he was graduated from high school. He was drafted during the war but rejected because of his heart disease. At the age of 28 years he passed a life insurance examination and received a standard policy. He always had a great deal of trouble overcoming respiratory infections. All of the doctors who examined him reported prominence of the left chest, a "bad heart," a slow pulse rate, and a normal blood pressure.

On March 6, 1938, he noticed slight redness and tenderness of the tip of his nose. By March 8 the condition of his nose had grown worse, and at noon he went home and applied moist heat. About 5 P.M. he became feverish and short of breath and developed pain in the right lower chest.

Examination that evening showed a well-developed and well-nourished, acutely ill man, about 50 years old, propped up in bed. His temperature was 103° F., his pulse rate 78, and his respiratory rate 36. The nails and mucous membranes were very cyanotic. The cheeks were flushed and slightly cyanotic. The tip of the nose was swollen, red, and somewhat indurated. The left side of the chest was more prominent than the right. The apex impulse of the heart was visible and palpable in the fifth intercostal space, and was diffuse in character, with its maximum intensity between 2 and 3 cm. outside the nipple. Along the left border of the sternum there was a rough systolic murmur with its maximum intensity in the second and third intercostal spaces. This murmur could also be heard at the apex, but not at the base of the neck. In the right axilla there was a patch of persistent, moist râles, with roughened bronchovesicular breathing. His blood pressure was 112/76. The remainder of the examination revealed nothing abnormal. There was no clubbing of the fingers or toes.

On the following morning he was obviously worse. The cyanosis was more marked and he was listless and drowsy. The swelling of the tip of the nose was less but there was swelling over the bridge of the nose and about the eyes. The hemoglobin was 111 per cent, the erythrocyte count 5,410,000, and the leucocyte count 6,600; 74 per cent of the leucocytes were polymorphonuclears. The urine was normal. By evening the patient's neck was slightly stiff and a few dark petechiae were noted on the left ear. The pulse rate varied between 78 and 110, dropping once to

54, the respiratory rate varied between 20 and 30, and the temperature between 101° F. and 104° F. On the morning of March 10 he could not be aroused. There were firm edema of the eyelids, chemosis, and left-sided exophthalmos. The entire body was covered with almost black hemorrhagic spots varying from 1 to 3 mm. in diameter. There were marked cervical rigidity, bilateral Kernig signs, and bilateral Babinski signs. A roentgenogram of the chest showed enlargement of the heart and diffuse mottling of the lung fields. The enlargement of the heart was toward the left. The left upper border was quite straight and there was no shadow in the region of the great vessels to the right of the midline. Death occurred at 5:15 p.m., approximately forty-eight hours after the patient went to bed.

Autopsy was performed (by A. V.) three hours after death. Only the thorax and abdomen were opened.

The pleura of the right lower lobe was covered with adherent fibropurulent material and the adjacent pleural cavity contained 300 c.c. of cloudy, flaky fluid. Throughout both lungs there were numerous yellow abscesses, some of which measured as much as 3 or 4 mm. in diameter. Both lower lobes showed confluent bronchopneumonia and, in addition, the right lower lobe contained several recent hemorrhagic infarcts. There was also purulent tracheobronchitis.

The liver weighed 2,500 gm. It presented a typical nutmeg appearance and showed throughout its substance numerous miliary abscesses similar to those found in the lungs. The bile ducts and gall bladder were normal. The spleen weighed 300 gm. Its capsule was thin, its consistency firm, its color bluish-red, and there were miliary abscesses throughout the pulp. The kidneys were normal in size and shape, but on section showed marked cloudy swelling and contained great numbers of miliary abscesses. Similar abscesses were present in the prostate. The other abdominal organs showed only passive hyperemia.

The pericardium was somewhat distended and contained about 50 c.c. of a cloudy, reddish-yellow fluid. The heart was enlarged, weighing 550 gm., and was obliquely egg-shaped. The aorta was large and emerged anteriorly and somewhat to the right, while the pulmonary artery was small and emerged from behind the aorta. The apex was formed predominantly by the right ventricle. There were numerous petechiae and miliary abscesses in the epicardium.

The right auricle was dilated, its endocardium was diffusely thickened, and the pectinated muscles were prominent and thick. It received the inferior and superior venae cavae and the coronary sinus normally. The eustachian and thebesian valves and the limbus were well formed. The fossa ovalis was incompletely closed, leaving anteriorly an elliptically-shaped vertical opening measuring 8 mm. in width. The foramen ovale was patent, admitting a rod 2 cm. in diameter. The tricuspid orifice was of normal size, and its leaflets were well formed, thin, and smooth. Their papillary muscles were hypertrophied. The wall of the right ventricle measured 2 cm. in thickness. Its cavity was considerably larger than that of the left ventricle and it occupied the greater part of the apex. From the posterior upper part of the right ventricle emerged the pulmonary artery. The right ventricle was only incompletely separated from the left by a muscular ridge, which almost completely framed a large opening between the ventricles. This opening was of an obliquely oval shape and measured from 2.5 to 3.5 cm. in diameter. The muscle ridge at its uppermost, arch-shaped portion measured 2.5 cm. in thickness, and at its anterior and lowest portion 2.2 cm. in thickness. It projected into the ventricle from 1.5 to 2 cm. Its uppermost, arch-shaped portion was situated behind and to the right of the aortic orifice and anteriorly and to the left of the pulmonary orifice, extending about 2.5 cm. below the level of their valves. From this arch two limbs extended: a right limb descending along the anterior wall of the ventricle obliquely to the left and ascending again along the posterior wall for a short distance, and a shorter left

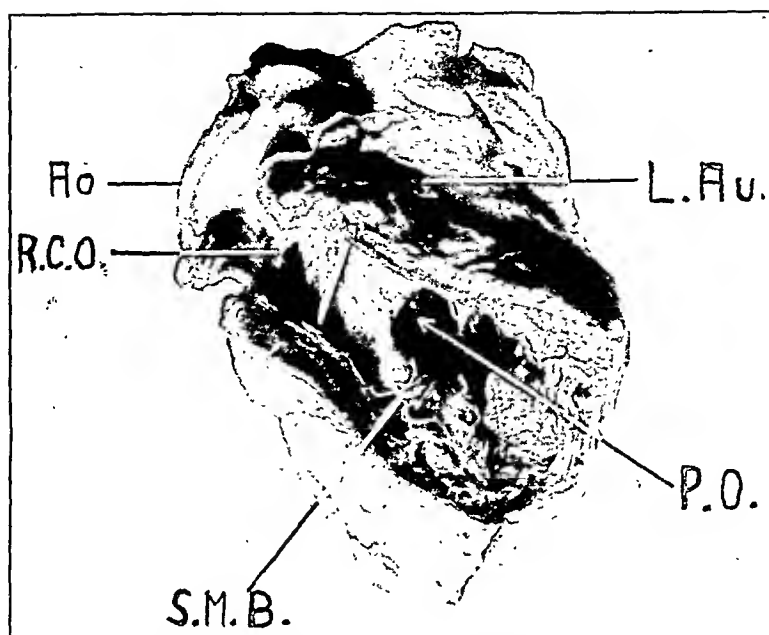


Fig. 1.—Photograph of heart from anterior aspect. Aorta and aortic conus opened. *Ao*, aorta; *L.Au.*, left auricle; *R.C.O.*, right coronary orifice; *P.O.*, pulmonary orifice, seen through septal defect; *S.M.B.*, septal muscle bundle.

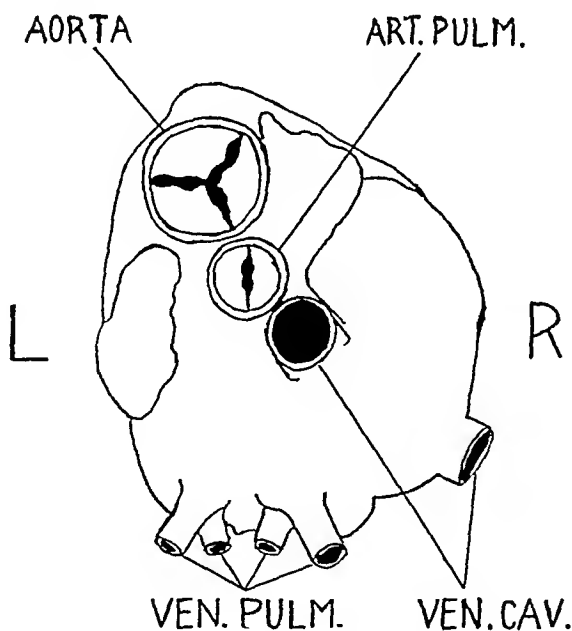


Fig. 2.—Schematic view of the heart from above.

limb which also descended obliquely along the anterior wall almost to the base of the anterior mitral cusp. Posteriorly and to the right of the muscular arch, adjoining and to the right of the aortic cusp of the mitral valve, and to the left of the left cusp of the tricuspid valve, was the pulmonary orifice. It possessed only two cusps, one left and anterior, and one right and posterior. The diameter of the pulmonary orifice measured 1.2 cm., while the greatest width of the elliptical opening between the cusps measured 5 mm. The aortic orifice measured 2.5 cm. in diameter and was situated anteriorly and to the left of the muscular arch. It possessed three cusps, an anterior and a right and left posterior. The noncoronary cusp was situated anteriorly. The ductus arteriosus was obliterated. There was no coarctation of the aorta. The branches of the aortic arch were normal. The mitral orifice was of normal width and its cusps revealed only a few flat, arteriosclerotic plaques. In addition to its normal attachment, the aortic cusp of the mitral valve was also attached to the left posterior portion of the muscular ridge. The wall of the left ventricle measured 2.4 cm. in thickness. The endocardium of the left auricle was slightly, but uniformly, thickened. Numerous petechiae were seen throughout the endocardium. The distribution of the coronary arteries was normal, although they were somewhat rotated to the left. The anterior descending branch of the left and the circumflex branches of both coronary arteries showed distinct thickening of the intima and media and narrowing of their lumina. The myocardium was of a yellowish-red color and revealed on section numerous firm, gray-white streaks and patches and very many yellow miliary abscesses similar to those seen in the other organs.

Anatomic Diagnoses.—Cor triloculare biatriatum; incomplete transposition of the aorta; stenosis of the pulmonary orifice; congenitally bicuspid pulmonic valve; absence of the ventricular septum; hypertrophy of the crista supraventricularis and of the septal and parietal muscle bundles; marked hypertrophy of the heart, particularly of the right ventricle; coronary sclerosis; chronic passive hyperemia of the lung, liver, spleen, etc.; petechiae and miliary abscesses in all organs, including the skin; multiple hemorrhagic infarcts and fibrinopurulent pleuritis of the right lower lobe; bilateral confluent bronchopneumonia.

COMMENT

It seems to us that this man had a furunculosis of the nose, whence the infection spread through the venous channels to produce thrombosis of the cavernous sinus and massive blood stream invasion.¹ The organisms in the various tissues examined after autopsy had the morphologic characteristics of staphylococci. Since an examination of the head was not permitted and cultures were not made, further discussion of this aspect of the case is fruitless.

A precise clinical diagnosis of the nature of the cardiac lesion was not made. When first seen the patient simply said that he had had heart disease since birth, and later he was in no condition to be questioned. He had not liked to talk about his heart and his wife was unfamiliar with his early history, most of which was obtained from an uncle after the patient's death. Without a history of early cyanosis and without clubbing of the fingers, which White and Sprague² state is invariably present in the tetralogy of Fallot, we were inclined to believe that he had a combination of interventricular septal defect and patency of the ductus arteriosus. The almost simultaneous ap-

pearance of what seemed to be pulmonary embolic phenomena and what were obviously systemic embolic phenomena required a veno-arterial shunt for their explanation. There was no evidence of sufficient change in the pulmonary circulation to open a previously patent but physiologically closed foramen ovale. We reasoned then that the crossed or paradoxical emboli must have occurred through a septal defect. The history of a slow pulse rate suggested auriculoventricular block and added weight to this idea.

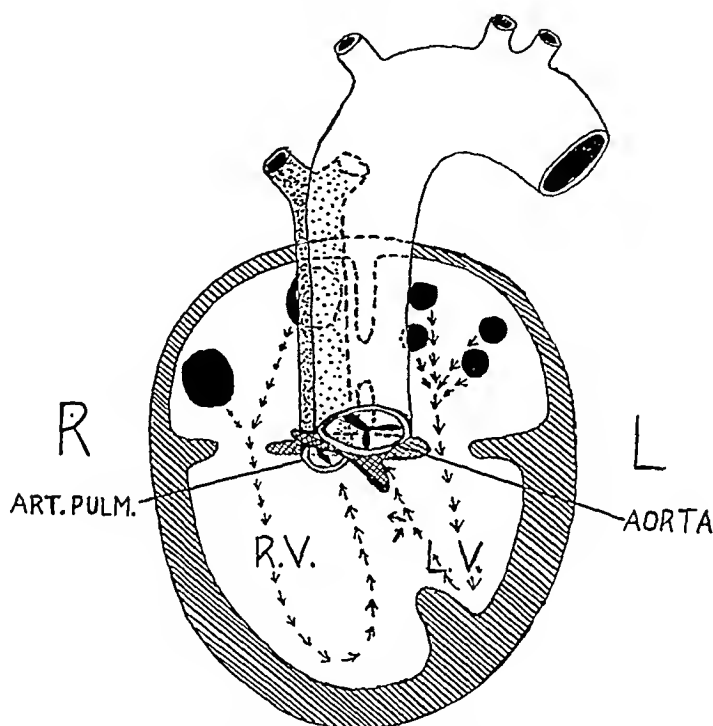


Fig. 3.—Schematic vertical section of the heart. Arrows indicate circulation when no congestive failure is present.

DISCUSSION

Fifty years ago Fallot³ stated that in congenital heart disease with cyanosis, particularly in adults, the possible malformations are small in number and perfectly definite. His observations have since been amply confirmed and this group is now termed the "tetralogy of Fallot." It consists of: (1) A stenosis or narrowing of the opening of the pulmonary artery at the valve cusps, or of the infundibulum just below them; (2) an interventricular septal defect; (3) dextro-position of the aorta; and (4) hypertrophy of the right ventricle. The course of the blood in such a heart is as follows: The venae cavae empty into the right auricle, from which the blood flows into the right ventricle; at this point the blood stream, obstructed by the narrow pulmonary orifice, only in part enters the pulmonary artery, the remainder going directly into the aortic orifice, which rides over the

interventricular septal defect and so receives blood from both ventricles. The right ventricle hypertrophies to accommodate itself to this increased work and the aorta is larger than normal. In the present case, however, there is evidence both from the history and the examination of the heart that the cardiac circulation was somewhat different. The muscular ridges described were directly in the path of the two streams of blood entering the common ventricle and were so situated that, under favorable hydrodynamic conditions, they would prevent any great mixing of arterial and venous blood (Fig. 3). The absence of cyanosis in similar cases has been noted before,⁴ and in this case the mechanism described may have been responsible for the unusually long span of life.

Although Fallot's article, written in 1888, is still thoroughly modern, most of the credit for the present interest in this condition and our ability to recognize it clinically belongs to Paul D. White. White⁵ lists five signs which, when they occur together, make the diagnosis of the tetralogy of Fallot practically certain. They are (1) cyanosis of lips, cheeks, ears, fingers, and toes, (2) clubbing of the fingers and toes, (3) a loud systolic murmur heard best in the pulmonary area and the third left intercostal space (at times accompanied by a systolic thrill), (4) marked right axis deviation in the electrocardiogram, and (5), roentgenographically, a sabot-like contour of the heart caused by enlargement of the right ventricle without enlargement of the pulmonary artery. The great vessels are prominent on the right as a result of dextroposition of the aorta, but not to the left because of the small amount of blood passing through the hypoplastic pulmonary artery. Another electrocardiographic finding of some value is auriculoventricular heart block, which might be a sign of congenital malformation of the intraventricular septum.

The congenital nature and interdependence of the anatomic changes noted in this and similar cases have been recognized for years, and a considerable literature dealing with the subject has accumulated. The view of the earliest observers, who believed that fetal endocarditis with subsequent stenosis of the pulmonary orifice and increased pressure in the right ventricle was the cause of the anomalies, has been abandoned. Since Rokitsansky's⁶ fundamental work it has been quite generally accepted that the pulmonary stenosis and the ventricular septum defect are consequences of the transposition, which in turn is due to abnormal development or rotation of the septum of the common arterial bulb. In 1923, Spitzer⁷ suggested a phylogenetic explanation of this process and presented evidence to show that it was a throwback to the period when vertebrates developed pulmonary respiration and two distinct circulations and had a right and left aorta originating from the respective ventricles. In these cases he thought that the phylogenetically atrophying and dormant right aorta

was reopened, while the left aorta was obliterated instead, primarily because of lack of torsion of the large vessels. This theory has since been doubted. Among others, Pernkopf and Wirtinger⁸ could find no proof for either an increasing degree of torsion in the higher classes of vertebrates or for the embryonal presence of even a temporary right ventricular aorta in mammals. More recently Lev and Saphir⁹ have given what seems to us a more satisfying answer. They believe that the essential process is an abnormal development of the bulboauricular spur which prevents the usual absorption of the arterial bulb into the left ventricle and thus a sufficient degree of normal clockwise rotation around this point. As a result, counter rotation of the unfixed lower end of the arterial bulb takes place, causing a more or less parallel, instead of spirally twisted, position of the aorta and pulmonary artery, and imperfect union or no union between the lower end of the aortic-pulmonary septum and the ventricular septum. They explain the pulmonary stenosis by the presence of a hypertrophic and rotated septal muscle bundle. Our case presents all of the anatomic evidences described by them, namely, the abnormally large bulboauricular spur, the misplaced septal and parietal muscle bundles, and the hypertrophy of both.

The prognosis in this type of malformation of the heart is usually bad. The average age at death in eighty-five cases reported by Abbott¹⁰ was 12½ years. However, the outlook may not always be so discouraging. The oldest patient in Fallot's original series was 36 years of age. Forty years later White and Sprague² reported the case of a man who died in his sixtieth year, and in 1936 McGinn and White⁵ mentioned a patient who was living at the age of sixty-two. At the present time, our patient seems to be the second oldest of those whose diagnoses have been proved by necropsy. He might have lived much longer but for an intercurrent infection. He had been active and self-supporting until forty-eight hours before his death.

SUMMARY

We have reported a case of congenital heart disease, the tetralogy of Fallot, in a man past 49 years of age who was active and self-supporting until his terminal illness. As far as we can determine, he is the second oldest patient known (autopsy) to have this disease. Death was due to sepsis following furunculosis of the nose and cavernous sinus thrombosis. In the terminal sepsis there were crossed or paradoxical emboli which passed through the septal defect.

REFERENCES

1. Maes, Urban: Infections of the Dangerous Area of the Face, *Ann. Surg.* 106: 1, 1937.
2. White, Paul D., and Sprague, Howard B.: The Tetralogy of Fallot, *J. A. M. A.* 92: 787, 1929.

3. Fallot, A.: Contribution a l'anatomie pathologique de la maladie bleue (cyanose cardiague), *Marseille Med.* 25: 77, 138, 207, 270, 341, 403, 1888.
4. Fleury, J.: Fallot's Tetralogy Without Cyanosis, *Arch. d. mal. du coeur* 30: 121, 1937.
5. McGinn, S., and White, P. D.: Progress in the Recognition of Congenital Heart Disease, *New England M. J.* 214: 763, 1936.
6. Rokitansky, C.: Die Defecte der Scheidewände des Herzens, W. Braumüller, Wien, 1875.
7. Spitzer, A.: Über den Bauplan des normalen and missbildeten Herzens, *Virehows Arch. f. Path. Anat.* 243: 81, 1923.
8. Pernkopf, E., and Wirtinger, W.: Das Wesen der Transposition im Gebiete des Herzens, ein Versuch zur Erklärung auf entwicklungsgeschichtlicher Grundlage, *Virehows Arch. f. Path. Anat.* 295: 143, 1935.
9. Lev, M., and Saphir, O.: Transposition of the Large Vessels, *J. Tech. Methods* 17: 126, 1937.
10. Abbott, Maude E.: The Diagnosis of Congenital Heart Disease, Part II, True "Morbus Caeruleus," in Blumer: *Bedside Diagnosis*, Vol. 2, p. 430, Philadelphia, 1928, W. B. Saunders Company.

CONTUSION OF THE HEART

REPORT OF A CASE WITH SERIAL ELECTROCARDIOGRAMS

LESLIE B. SMITH, M.D., AND HILTON J. McKEOWN, M.D.*
PHOENIX, ARIZ.

A REVIEW of the literature leads one to believe that nonpenetrating wounds of the heart occur rarely. Bright and Beck¹ (1935), in a search of the literature for cases of nonpenetrating wounds of the heart, collected only twelve cases of myocardial contusion in which recovery took place. There were 152 necropsy cases of rupture of the heart, and eleven cases of myocardial failure without rupture in which the diagnosis was established by necropsy. They give an outline of the various ways in which nonpenetrating wounds of the heart were produced.

Beck² reported three cases of nonpenetrating wounds of the heart, in one of which the diagnosis was proved by necropsy, and mentioned three additional cases. Kissane³ has collected and reported fifteen cases illustrating the varying degrees of cardiac contusion which may follow chest injuries. He found that there is usually a relationship between the severity and type of chest injury, but fatal contusion may occur without evidence of trauma to the chest wall. Stromer⁴ cites four cases of cardiac contusion, including Hadorn's case, that of a 13-year-old girl who suffered contusion of the heart, in which the electrocardiogram indicated a severe injury of the right side of the myocardium. We have at hand eight cases, other than the one reported here, in which both clinical and electrocardiographic evidence of myocardial damage appeared within twenty-four hours after blows to the chest. Moritz and Atkins⁵ have added another case in which the diagnosis was proved by necropsy. Barber⁵ mentions six men who had inefficient hearts after severe blows to the chest wall.

The recent experimental studies of Bright and Beck,¹ Moritz and Atkins,⁶ and especially of Kissane, Fidler, and Koons⁷ have thrown considerable light on this subject; Kissane, and others, injured the hearts of dogs by striking the chest wall over the heart, without opening the chest wall. White and Glendy,⁸ in a very comprehensive discussion of "Trauma and Heart Disease," have cited the experimental works of Klubs (1909), Klubs and Strauss (1932), and Schlomka (1934), and have discussed many of the facts and theories pertaining to nonpenetrating wounds of the heart.

Barber⁵ states: "Trauma of the heart may result (1) from wounds and direct violence, and (2) from strain of effort . . . direct violence to

*From the Section of Internal Medicine, Lois Grunow Memorial Clinic, Phoenix, Ariz.

Received for publication Oct. 17, 1938.

the chest wall may rupture the heart muscle, causing death, or may cause death without obvious heart injury; or it may give rise to the following clinical conditions: (1) pericarditis; (2) angina of effort; (3) a disorder of rhythm; (4) lesions of a valve; (5) contusion of the heart muscle. Strain may result in: (a) a disorder of rhythm; (b) lesions of a valve; (c) primary cardiac overstrain."

It is now well established that trauma may give rise to cardiac contusion, varying in degree from small bruises with slight or no clinical evidence of damage to rupture of the heart wall, even though the blow to the chest may have appeared to be slight. The cardiac impairment following a contusion may clear up completely, or various degrees of impairment may be present for a short time, or for years.

The following case is reported because it demonstrates clearly the possibility of damage to the myocardium from external forces applied to the chest, even though the latter did not leave any evidence of damage to the chest wall. We also believe that this is the first case of trauma to the heart to be reported in which a serial electrocardiographic study was made. It is our opinion that contusions of the heart too frequently are not recognized by physicians, or by our courts and insurance companies.

CASE REPORT^{*}

P. R., a white 17-year-old high school student, had always enjoyed good health. On March 1, 1938, in the course of a routine examination, an electrocardiogram (Fig. 1) and a tereoroentgenogram of his chest were made, both of which were normal.

The patient was injured April 10, 1938, in an automobile collision involving the car he was driving and a truck. It was reported that the patient's chest had struck the left car door sufficiently hard to make an imprint in the door. In this accident he received several lacerations of the scalp and two small puncture wounds about the right elbow. There was only a small visible contusion of the chest, over the right lower ribs anteriorly, with no fractured ribs. The skin wounds were negligible except for a mild, secondary, staphylococcus infection in the puncture wounds, which healed within two weeks.

In the first twenty-four hours he was quite irrational at intervals; however, there were no other evidences of cerebral injury. The hemoglobin was 84 per cent (Sahli). The leucocyte count was 13,800, of which 71 per cent were neutrophilic polymorphonuclear cells, 22 per cent lymphocytes, and 8 per cent monocytes.

During the first forty-eight hours the patient's rectal temperature gradually rose to 102.5° F., and his pulse rate varied from 76 to 100 per minute, being in the upper eighties and nineties most of the time. The blood pressure varied from 100/80 to 136/90. He was irrational at frequent intervals and was very restless. On the third day he began to complain of severe "gas pains," although elimination through the bowels was satisfactory and there were no evidences of abdominal distention. He also complained of some pain in the left anterior chest. On the fourth day the pain in the left anterior chest was quite severe for several hours and restlessness became more marked. The pulse rate ranged from 88 to 100 per minute.

The patient was first seen by one of us (L. B. S.) on the fourth day following the accident. At this time physical and roentgenologic examination revealed noth-

^{*}We are indebted to W. O. Sweek, M.D., and H. G. Williams, M.D., for their cooperation in reporting this case.

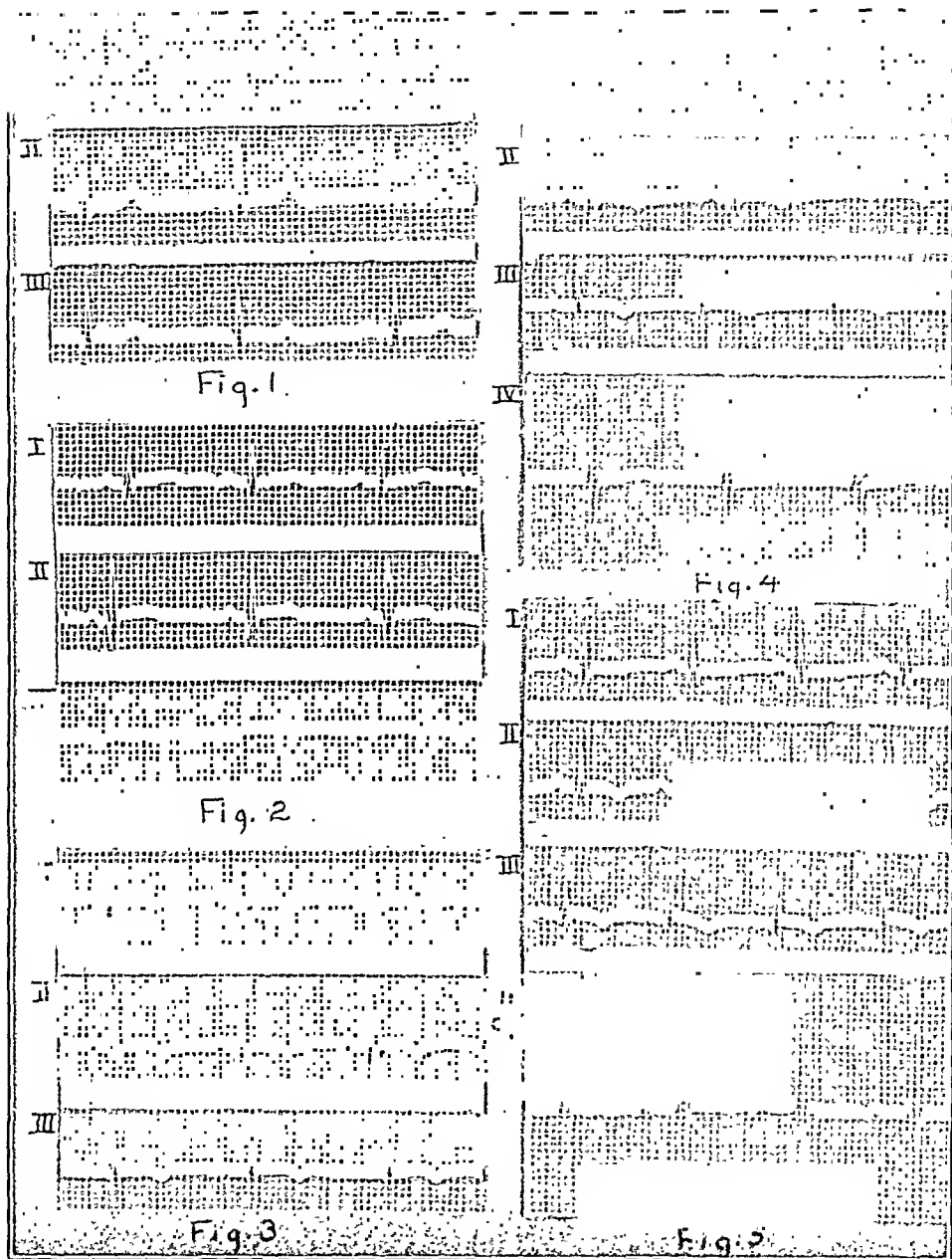


Fig. 1.—Normal. Taken March 1, 1938, 6 weeks prior to accident.

Fig. 2.—Eleven days after the accident and four days after the onset of the precordial pain. QRS, decreased voltage; RS-T, moderately elevated and has a "humped up" effect in all three leads; T_2 and T_3 , slight negativity. Taken April 21, 1938, eleven days after injury.

Fig. 3.— T_1 , slightly negative. T_2 and T_3 , more negative. April 25, 1938.

Fig. 4.— T_1 , isoelectric. T_1 is notched and of lower amplitude than in Lead IV taken six days previously. There has been a slight lessening of the voltage of the QRS in Leads I, II, and III. May 4, 1938.

Fig. 5.—ST₂ sloping downward to an inverted T; Lead III, sloping of ST more marked. T_1 , initial negativity. May 12, 1938.

ing abnormal in the lungs. The temperature was 100° F., the pulse rate 100, the rhythm normal, and the blood pressure 100/70. There was no cardiac enlargement. No thrills could be felt. Auscultation revealed that the heart sounds had a peculiar ticktack quality, as if the heart were under strain. At this time it was thought that there was some cardiac involvement. The leucocyte count was 13,200, of which 90 per cent were polymorphonuclear cells, 1 per cent eosinophiles, 1 per cent monocytes, and 8 per cent lymphocytes.

During the next three days the patient's temperature returned to normal. His systolic blood pressure varied from 100 to 110, with a diastolic of 70 to 80. He made occasional reference to discomfort in the region of his heart, but the discomfort in his abdomen had subsided.

On April 17, 1938 (seventh day), following an afternoon of mild physical exertion, he was seized suddenly by a severe pain in the left chest which he described as originating under his left shoulder blade and shooting through to the front of the chest. The pain was continuous, excruciating, and lancinating in character, and was associated with a sensation of breathlessness. He was very apprehensive and restless. Codeine was given for the pain, but it did not begin to lessen for three hours and continued, with varying intensity, for thirty-six hours. During this time he complained of severe pains in the region of second and third left ribs, just lateral to the sternum, and also in the left shoulder and in the left side of his neck, with an occasional extension of the pain to the right side of the neck and right shoulder. Examination of the heart at the time of the onset of the pain and twelve hours later revealed no abnormal findings except that the heart sounds were "labored." The temperature was 99° F., the pulse rate 90 to 100, and the blood pressure 130/70. The leucocyte count was 9,850, of which 62 per cent were polymorphonuclear cells, 33 per cent lymphocytes, 2 per cent eosinophiles, 1 per cent basophiles, and 2 per cent monocytes. Roentgenograms of the chest showed no definite abnormality of the lungs.

Twenty hours after the onset of pain a very definite, loud, pericardial friction rub was heard, of maximum intensity over the second and third left intercostal spaces, just lateral to the sternum. By this time the pain was synchronous with the heart beat, and was aggravated by expiration. At about this time the pain became localized in the region of the base of the heart, with frequent sharp pains in the left shoulder and under the left shoulder blade. The pulse rate was 90 and the temperature 99° F. The blood pressure had dropped to 90/60.

Twelve hours after the first time the pericardial friction rub was heard it disappeared, and was never detected again by frequent examinations. The pain took on an aching character and subsided thirty-six hours after the onset, at which time the pulse rate dropped to 72. The blood pressure remained low during the thirty-six hours of pain, then returned to normal. During the course of the pain the temperature never went above 99.2° F.

A soft, systolic murmur was heard over the second right intercostal space at various times, but not constantly, during the first four weeks.

The patient was kept at rest in bed for six weeks, and was first allowed to be up on May 25, 1938. The remainder of his convalescence was uneventful, except for an occasional attack of dizziness lasting for a few minutes. The temperature, pulse rate, and blood pressure remained normal.

A diagnosis of contusion of the heart was made when the pericardial friction rub appeared, and this was confirmed by the first electrocardiogram (Fig. 2), taken four days after the onset of the precordial pain.

The laboratory findings, other than the electrocardiograms, during the convalescence were as follows: April 25, leucocyte count, 14,100; polymorphonuclears, 80 per cent; lymphocytes, 17 per cent; monocytes, 1 per cent; eosinophiles, 1 per cent;

basophiles, 1 per cent; April 28, sedimentation rate of erythrocytes, 22 mm. in sixty minutes. May 4, leucocyte count, 8,350; polymorphonuclears, 54 per cent; lymphocytes, 35 per cent; eosinophiles, 6 per cent; monocytes, 5 per cent; the blood Kahn and Wassermann reactions were negative. A roentgenogram of the chest showed that both pulmonary fields were clear and free from abnormal shadows; the heart was apparently normal in size, contour and location. May 12, leucocyte count, 6,100; poly-

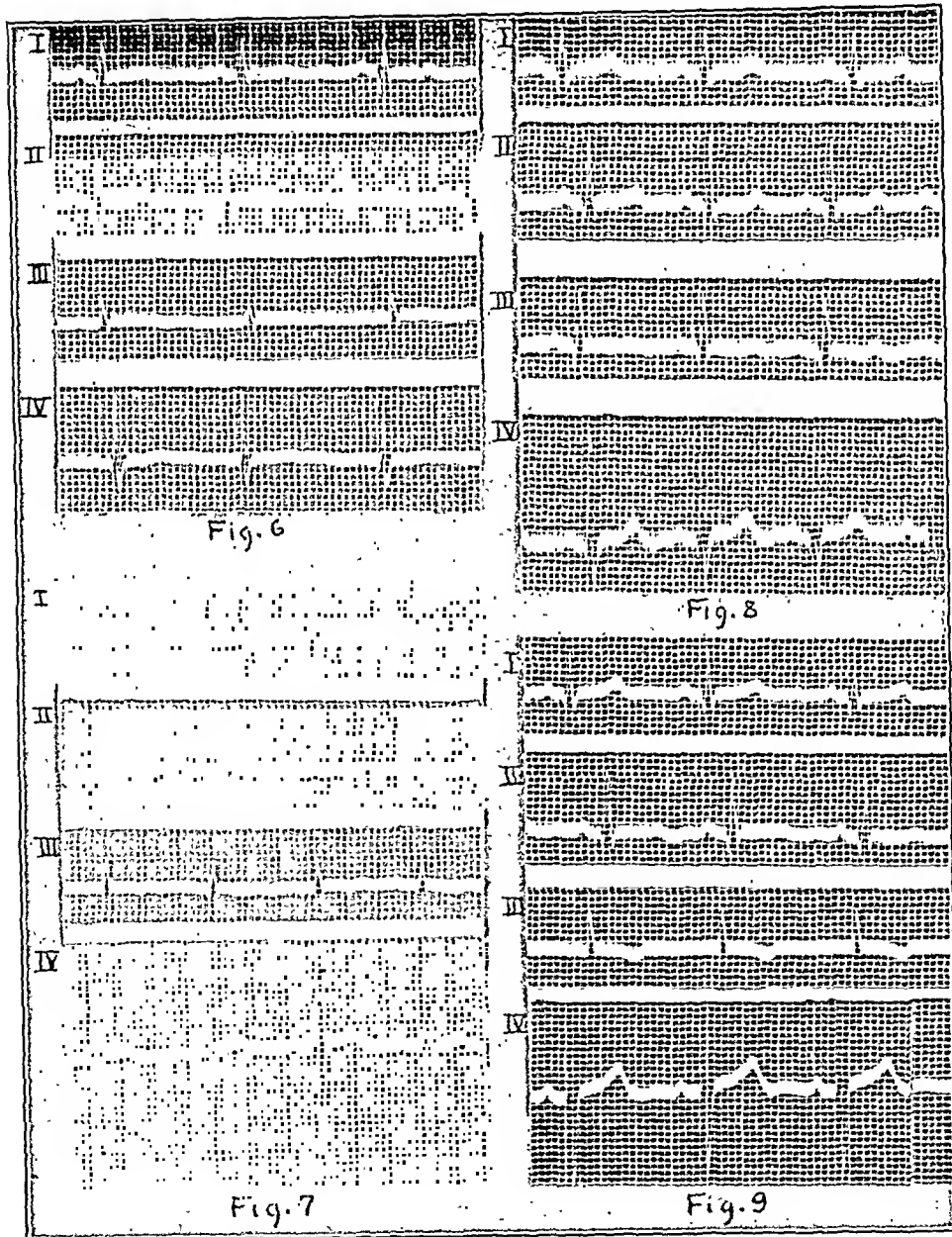


Fig. 6.—Q₁, deeper; T₁, low voltage but positive; T₂, diphasic; T₃, isoelectric; S₁, greatly reduced; T₄, low voltage (S₁, seven days later showed an increase in voltage, but still reduced.) May 19, 1938.

Fig. 7.—T₁, 2, 3, 4, more positive; S₁, increased in voltage. June 1, 1938.

Fig. 8.—Within normal limits, except lessened voltage of S₁. June 13, 1938.

Fig. 9.—T₂, lower voltage. Downward sloping ST₂ with inversion of T₂, RS-T₂, elevated with upward slope. July 28, 1938.

morphonuclears, 56 per cent; lymphocytes, 35 per cent; eosinophiles, 3 per cent; basophiles, 1 per cent; monocytes, 5 per cent; erythrocyte sedimentation rate, 15 mm. in sixty minutes. On June 6 roentgenographic and fluoroscopic examination revealed that no appreciable changes had occurred in the heart since the preceding examination, including that of March 1, 1938, prior to the accident. During convalescence there were no physical or roentgenologic evidences of pericardial effusion. The electrocardiograms are presented below.

Graded physical activities were started on May 25, 1938, and he has been ambulatory since the first week of June, 1938. On July 26, 1938, his physical activities were still limited to short walks. He was unable to indulge in any moderately strenuous physical activities without undue fatigue and persistent increase in pulse rate. Even though the last two electrocardiograms (Figs. 8 and 9) are apparently normal, this patient still had a functional cardiac impairment fifteen weeks following the accident.

He was last examined Sept. 9, 1938, at which time his recovery was almost complete. The pulse rate and blood pressure responses to exercise tests were within normal limits, and radiographic study revealed no abnormalities. The vital capacity was 93 per cent of normal. An electrocardiogram taken on this date shows in Lead III a slight elevation of the RS-T segment, which slopes down to a negative T wave. This RS-T slope, we believe, is a residual effect of the scarring of the myocardium.

A series of twelve electrocardiograms was taken in this case. Three have been omitted because of their similarity to preceding tracings. In the legends, only the serial changes of significance, in sequence, are mentioned; all electrocardiograms were standardized.

DISCUSSION

The serial electrocardiographic changes in this case are similar to those which we have learned to associate with pericarditis.* We believe that if an electrocardiogram had been taken a few days earlier the elevation of the RS-T segment would have been much higher, since it is known that the higher elevations of the RS-T may be transient.

We believe that trauma was the cause of the friction rub in this case. That nonbacterial pericarditis may be caused by trauma is established. Bright and Beck¹ cited two cases from the literature in which death did not occur, and Beck² reports another case in which a pericardial friction rub developed. All of these patients had nonpenetrating wounds of the heart. Bright and Beck, in their experimental work, found that fourteen of the seventeen dogs coming to autopsy two to three months after direct trauma to the heart had adhesions between the pericardium and epicardium. Kissane, and co-workers,⁷ who found that they could damage the hearts of dogs by striking the chest wall over the heart, state: "The most frequent cardiac lesions were subendocardial and subpericardial hemorrhage . . . pericardial injury and tear with or without free blood in the pericardial sac."

*We wish to thank Dr. Thomas Dry, who saw this patient in consultation two weeks following the accident, and Dr. Arlie R. Barnes, of the Mayo Clinic, who has concurred with our interpretation of the serial electrocardiograms, for their interest in this case.

Infectious pericarditis is rendered unlikely by the fact that the patient had no fever, only a slight leucocytosis, and no appreciable pericardial effusion.

There remain, in our opinion, only the following possibilities, namely, that the accident produced: (1) primary damage to the pericardium or epicardium, (2) primary contusion of the subepicardial myocardium with a secondary plastic pericarditis similar to the nonpurulent pericarditis which frequently follows cardiac infarction, or (3) a combination of these two. The idea that the primary damage was to the myocardium is in keeping with the recently reported findings of Bellet and McMillan⁹ concerning the electrocardiographic pattern in pericarditis; they state: "Only when there was demonstrable myocardial damage was deviation of the RS-T segment noted." They interpret their findings, and cite the opinions of others, ". . . as supporting the view that the striking deviation of the RS-T segment associated with certain forms of acute pericarditis is the result of myocardial change that is gross enough to be demonstrable histologically." This view is further supported by the similarity between the electrocardiographic findings in the nonpurpurative pericarditis caused by infarction of the subepicardial myocardium and those in acute bacterial pericarditis.

In their experimental study of contusion of the heart, Moritz and Atkins⁶ found that "many of the myocardial changes seen in this series of dogs with cardiac contusion bore striking resemblances to the gross and microscopic changes seen in myocardial infarction in man."

Kissane, and co-workers,⁷ found changes similar to those produced by experimental coronary occlusion. The experimental and clinical studies of Bright and Beck^{1, 2} indicated that "the most frequent variations from the normal was the production of large T waves and alterations in the Q wave. Frequently there was a high take-off of the T wave; sometimes the T was inverted." Kissane, et al.,⁷ found that the most frequent electrocardiographic changes were "in the T waves and RS-T components. . . ." Since contusions may be located in any part of the heart and involve any number of areas, the electrocardiographic changes may be quite bizarre and fit no definite known pattern. It must not be forgotten that trauma may produce serious disturbance in rhythm without any demonstrable lesion.

The diagnosis of contusion of the heart will remain difficult when the patient is in the "coronary age" and recovers. Cardiac trauma may be superimposed on any type of heart disease, and in such cases the role of the trauma may be most difficult to determine. We must recognize that a diseased heart is more vulnerable, and that the disease which exists prior to the trauma is readily aggravated or complicated by it. It is the development of new cardiac signs and symptoms or the accentuation of pre-existing signs or symptoms after trauma that establishes the role of the trauma. The most important diagnostic criteria are enlargement of

the heart as shown by roentgenograms, and serial changes in the QRS, the RS-T segment, or the T waves of the electrocardiogram.

It is our opinion that a diagnosis of traumatic heart disease is justified when a patient receives either a direct or an indirect blow to the chest, or undergoes undue physical strain, or is subjected to other types of external violence, and then develops, without other apparent cause, circulatory embarrassment, or other clinical or electrocardiographic signs of heart disease.

CONCLUSIONS

1. A case of contusion of the heart, with recovery, in a 17-year-old boy, including a serial electrocardiographic study, is presented.

2. Although the electrocardiograms present a pattern that may be associated with pericarditis, in this case the primary damage was to the myocardium and the nonbacterial pericarditis was secondary.

3. Contusion of the myocardium in this case was produced without evidence of any damage to the chest wall.

4. Contusion of the heart is discussed briefly.

5. We believe that cardiac contusions, in this automobile age, are too frequently overlooked.

REFERENCES

1. Bright, Ernest F., and Beck, Claude S.: Non-Penetrating Wounds of the Heart, *AM. HEART J.* 10: 293, 1935.
2. Beck, Claude S.: Contusion of the Heart, *J. A. M. A.* 104: 109, 1935.
3. Kissane, R. W.: Contusion of the Heart, Ohio State University, Columbus, Ohio. Lecture at Fourth Post-Collegiate Assembly, 1937.
4. Stromer, A.: Traumatic Diseases of the Heart, *Deutsche med. Wchnschr.* 64: 235, 260, 1938.
5. Barber, Hugh: Trauma of the Heart, *Brit. M. J.* 1: 433, 1938.
6. Moritz, Allan R., and Atkins, Joseph P.: Cardiac Contusion, *Arch. Path.* 25: 445, 1938.
7. Kissane, R. W., Fidler, R. S., and Koons, R. A.: Electrocardiographic Changes Following External Chest Injury to Dogs, *Ann. Int. Med.* 11: 907, 1937.
8. White, P. D., and Glendy, R. E.: In "Trauma and Disease" by Leopold Brahdy and Samuel Kahn, Philadelphia, 1937, Lea & Febiger.
9. Bellet, Samuel, and McMillan, Thomas M.: Electrocardiographic Patterns in Acute Pericarditis, *Arch. Int. Med.* 61: 381, 1938.

CARDIAC ANEURYSM

LOUIS H. BERK, M.D.*

NEW YORK, N. Y.

ALTHOUGH cardiac aneurysms are often found post mortem, very few cases have been reported in which the diagnosis was made clinically and confirmed by necropsy. The reason for the failure to make the diagnosis of cardiac aneurysm is that there are no constant clinical or roentgenologic signs characteristic of the condition. A comparison of the clinical and radiologic signs with the autopsy findings has permitted us to make several observations regarding the diagnosis of cardiac aneurysm.

Cardiac aneurysm is merely a mechanical result of the fibrous transformation of the myocardium. The condition was first studied by Ziegler,¹ and Cohnheim and Schulthess-Reehberg,² in 1881, who introduced the concept that the formation of a cardiac aneurysm could be traced to myocardial ischemia. More extensive studies were made by Hall,³ who in 1903 reported 112 cases and gave a more complete picture of the pathogenesis of such aneurysms. Sternberg,⁴ in 1914, wrote a monograph which has since been accepted as the authoritative work on the subject. He predicted that the roentgenologic diagnosis would be possible, described the typical course of aneurysm formation, and brought forth the concept of chronic partial cardiac aneurysm, distinguishing four stages, as follows: (1) the stage of attacks of cardiac pain, often of very short duration; (2) the stage of localized pericarditis at the site of infarction, occasionally producing a pericardial friction rub of only a few hours' duration; (3) the stage of latency, or apparent cure, lasting several weeks to many years; and (4) the stage of advanced myocardial disease, associated with chronic hydrops or leading to rupture.

Kraus,⁵ in 1919, first reported the correlation of the post-mortem and roentgenologic findings. Since that time the European literature has contained reports of isolated cases, and a few articles have appeared in the American literature, the most recent being those of Sigler and Schneider,⁶ Steel,⁷ and Ball.⁸

The development of myocardial aneurysm is logically explained by pathologic changes resulting from a slowly produced obstruction of a coronary artery of the heart by arteriosclerosis, often completed by thrombosis. Such obstruction causes gradual wasting of the cardiac muscle and its replacement by fibrous tissue. In this scarred area the wall of the heart becomes much thinner, and as healing progresses it may

*Bellevue Hospital (Columbia University). First Medical Division, Dr. I. O. Woodruff, Director, and the Department of Laboratories, Dr. D. Symmers, Director.
Received for publication Oct. 18, 1938.

become stretched until a saccular dilatation is formed. Thrombi are frequently formed on the inner surface of the sac. If the scar is strong enough to resist the intraventricular pressure, no bulging beyond the line of the epicardium will take place. Such a lesion is termed a partial cardiac aneurysm. If there is a local weakening of the cardiac wall, which then yields to the intracardiac pressure, bulging beyond the line of the epicardium occurs and a chronic cardiac aneurysm is formed. Although aneurysm of the left ventricle may weaken the cardiac wall to the point of yielding, its strength is frequently augmented, and bulging prevented, by the presence of pleuropericardial adhesions, thickening of the epicardium, or thrombus formation within the aneurysmal sac.

The site of cardiac aneurysm is most commonly at the apex of the ventricle, or in the anterior wall immediately above the apex. This marked predilection for the apex is accounted for by the fact that it is the part furthest removed from the blood supply and is the thinnest part of the left ventricle. The larger and older aneurysms naturally involve more of the ventricular wall. The size of these dilatations is rather variable and depends to some extent upon the age of the aneurysm. The causes of death following cardiac aneurysm are: the effects of an embolism derived from a mural thrombus, a severe hemorrhage caused by rupture of the aneurysm, or cardiac failure.

Coronary obstruction is the chief causative factor of cardiac aneurysm, although in a few cases it is reported to have arisen from gummas, ulcerative endocarditis, trauma, or from an abscess or cyst in the heart wall.

CLINICAL FINDINGS

It is a rather curious fact that cardiac aneurysms are rarely manifested by signs peculiar to themselves. Lutembacher⁹ stresses the importance of fixation of the apex due to pericardiodiaphragmatic adhesions and localized tenderness over the adhesions. This circumscribed tenderness occurs on digital pressure and persists throughout life. The apex is immobilized by adhesions, as shown by palpation and percussion carried out successively in the right and left decubitus. Displacement of the left border of the heart sometimes simulates displacement of the apex. The precordial pulsations are poorly perceived, although the entire myocardium contracts vigorously.

Frequently, in cases of cardiac aneurysm, the heart beat is feeble, with a diffuse, heaving cardiac impulse, weak heart sounds, and cardiac enlargement. The coexistence of hypertension does not preclude the possibility of cardiac aneurysm. Often there are two palpable cardiac impulses—the true, forceful apex beat, and the heaving contraction of the aneurysmal sac. This has been noted previously by Harvier and Caroli,¹⁰ and by Christian and Frik.¹¹ Libman¹² stresses the presence of a pulsation, separate and distinct from the apical pulsation and associated with a dull first sound and gallop rhythm, as pathognomonic of aneurysm. In

only one of our cases did we find displacement of the apex beat (Case 1), and in only one case did we find a heaving pulsation over the entire precordium (Case 9). The heart sounds were often distant and muffled, and of poor muscular quality. A soft, apical, systolic murmur was frequently found. There was nothing characteristic about the manifestations of cardiac insufficiency in patients having cardiac aneurysm. However, these manifestations merit our attention because of their abrupt appearance following coronary occlusion and the difficulty with which compensation is re-established. These patients frequently had repeated attacks of congestive failure and pulmonary infarction. These may be the only noteworthy features of cardiac aneurysm. Some patients are surprisingly well, considering their disease. One patient (Case 1) had recurrent attacks of paroxysmal nocturnal dyspnea and pulmonary infarction for a period of six years, and finally succumbed to a massive pulmonary infarct.

RADIOLOGIC FEATURES

In the last four years there has been a considerable increase in the number of cases of aneurysm of the left ventricle in which the aneurysm has been visualized roentgenographically in vivo, and its presence later confirmed by necropsy. Since cardiac aneurysms are found at necropsy in at least 9 per cent of cases of cardiac infarction (Levine,¹³ Parkinson and Bedford,¹⁴ Zadek,¹⁵), we can reasonably expect to find them not infrequently in many cases of coronary thrombosis. Because the clinical manifestations of cardiac aneurysm are rather indefinite, we have come to value the roentgenologic examination as not only helpful but of decisive importance.

Roentgenograms should be made in the anteroposterior and oblique positions, and there should be a fluoroscopic examination. Oblique examination from a series of slightly different angles is indispensable in discovering aneurysms that have developed upon the ventricular surface, especially when they are small in size. Examination in the oblique position offers confirmation that at all points the aneurysm is an integral part of the heart. Measurement of the index of depth, when combined with oblique examination, makes it possible to find the exact location of the aneurysm.

Cardiac aneurysms may be conveniently divided into two general types: (1) a diffuse type with an eccentrically dilated cardiac apex, and (2) a circumscribed dilatation with an oval or angular bulging.

The diffuse form is most frequently encountered. It is marked by an eccentrically dilated cardiac apex with a barely perceptible systolic contraction. The circumscribed type is less frequently seen. It is marked by an oval or angular bulge varying in size, and is most commonly situated at the apex or midportion of the left cardiac border. The degree of pulsation is directly proportional to the size of the aneurysm, and varies inversely with the amount of pericardial thickening and the

presence of adhesions or mural thrombi within the aneurysmal sac (Boller and Pape¹⁶). Large aneurysms will occasionally show a passive, pulsatory, postsystolic lagging, as in the case reported by Kalisch,¹⁷ and in the case in which Lenk¹⁸ observed no marked pulsation during systole.

Sometimes the hypertrophic myocardium adjacent to the border of the aneurysm appears as a marked prominence with systolic pulsations. This has been mistaken for the aneurysm itself, as in the case of Christian and Frik,¹¹ in which the bulging was diagnosed as the aneurysm because of its marked pulsation. The necropsy revealed only hypertrophic muscle at that point, while the aneurysm was situated elsewhere.

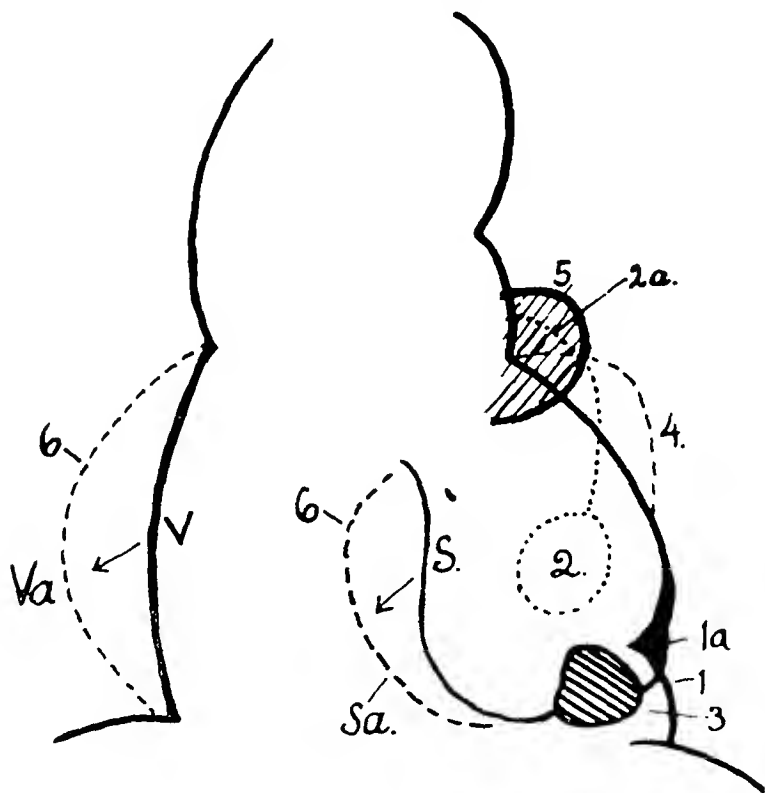


Fig. 1.—Schematic drawing showing various locations of cardiac aneurysms as seen roentgenologically by: Assmann, 1, 1a; Christian and Frik, 2, 2a; Jaksch-Wartenhorst, 3; Kalisch, 4; Brenner, 5; Boller, 6. V, Normal contour of right auricle; Va, displacement of the right auricular contour toward the right; S, normal interventricular septum; Sa, aneurysmal bulging of ventricular septum, causing displacement of right side of heart toward right.

Calcification of the aneurysmal wall, which occasionally occurs, appears as a curved line and produces a systolic and sometimes rotatory pulsation, as in the case reported by Jaksch-Wartenhorst.¹⁹ Brenner and Wachner²⁰ report a case of a large, calcified, saccular aneurysm of the left ventricle near the base, which is a most unusual location. Aneurysms of the ventricular septum can be visualized only if large enough to cause displacement of the right side of the heart toward the right (Boller).

Direct roentgenologic visualization will be impossible if a cardiac aneurysm develops on the diaphragmatic, hepatic, or posterior surface of the heart. The difficulty is increased if the aneurysm does not make

up a part of the left cardiac border, or if, due to adjacent pericardial thickening and adhesions, it does not show bulging or pulsations.

The presence of plenropericardial adhesions, with immobilization of the apex, which is clearly seen on the fluoroscopic screen, is an indirect corroborative sign of cardiac aneurysm. The cardiodiaphragmatic sinus may be filled with these adhesions. By means of radioecopy it is a simple matter to establish the fact that the site of the localized cardiac pain, which is increased by digital pressure in aneurysm of the left ventricle, corresponds to the location of these adhesions. Measurement of the bisector of the left ventricle reveals that it is uniformly increased. In the absence of concomitant hypertension, this demonstrates bulging of the left ventricular border which would not be apparent without measurement. It is particularly useful in revealing the diffuse type of aneurysm.

REVIEW OF CASES

In this paper we are particularly concerned with the ventricular aneurysms which were found in sixteen patients; the diagnoses were based on clinical and radiologic examination at Bellevue Hospital during the past four years, and on eight autopsies. Of our sixteen patients, eight are still living and under observation (Cases 9 to 16).

We present our cases in two groups. In Table I we report eight cases of cardiac aneurysm in which the patients were examined radiologically during life and the diagnoses later confirmed by necropsy. From the study of this series it would appear that the most important radiologic signs of cardiac aneurysm are the following: (1) diffuse, eccentrically dilated cardiac apex; (2) circumscribed oval or angular bulging of the left ventricular border; (3) presence of plenropericardial or diaphragmatic adhesions; (4) diminished systolic contraction in the aneurysmal zone; (5) calcification of wall of the sac.

In Table II (Cases 9 to 16) the diagnosis of aneurysm of the left ventricle was based on radiologic examination, together with a history and electrocardiographic findings of coronary occlusion. The examination of these patients, in the light of accepted clinical criteria, has revealed that the following are the most important clinical diagnostic signs: (1) history of coronary occlusion and congestive heart failure; (2) weak first heart sound; (3) cardiac enlargement (these three signs were found in 100 per cent of our cases); (4) diffuse, heaving, precordial impulse (87.5 per cent).

These features, together with the radiologic findings mentioned heretofore, warrant a diagnosis of cardiac aneurysm.

The following signs, though often mentioned in the literature, were less frequently seen in our cases: (1) expansile pulsation between apex and sternum (37.5 per cent); (2) disproportion between the force of the apex beat and the intensity of the heart sounds (50 per cent); (3) fixation of apex and localized precordial tenderness (12.5 per cent).

TABLE I

CASE	SEX	AGE	DIFFUSE ECCENTRICALLY DILATED CARDIAC APEX	CIRCUMSCRIBED OVAL OR ANGULAR BULGING OF LEFT VENTRICULAR BORDER	DIMINISHED SYSTOLIC CONTRACTION OF ANEURYSMAL ZONE	PRESENCE OF PLEURO- PERICARDIAL OR DIAPHRAG- MATIC ADHESIONS	CALCIFICATION OF WALL OF THE SAC	AUTOPSY FINDINGS
1	M	37	+	+	+	+	+	Concentric apical aneurysm with calcified mural thrombus covered by pleuropericardial adhesion. Multiple pulmonary, renal, and splenic infarcts.
2	F	67	+	+	+	+	+	Circumscribed saccular aneurysm 8 cm. in diameter in middle of left ventricle extending into interventricular septum.
3	F	70	+	+	+	+	+	Aneurysm of apex of left ventricle 7 cm. in diameter.
4	M	78	+	+	+	+	+	Diffuse dilatation of left ventricle near apex and posterior to interventricular septum extending upward 8 cm., filled with calcified mural thrombus.
5	M	69	+	+	+	+	+	Ruptured saccular aneurysm of left ventricle 4 cm. in diameter extending to within 2 cm. of apex. Sac partially filled with soft thrombus.
6	M	51	+	+	+	+	+	Saccular aneurysm of apex.
7	M	60	+	+	+	+	+	Diffuse bulging of anterior wall of left ventricle extending into the interventricular septum; pericardial adhesions.
8	M	49	+	+	+	+	+	Aneurysmal dilatation of left ventricle in region of apex and interventricular septum.

TABLE II

CASE	SEX	AGE	HISTORY		CLINICAL SIGNS								EKG CHANGES	RADIOLOGIC SIGNS						(NORMALY 1.2 TO 1.8 CM.)
			HISTORY OF CORONARY THROMBOSIS	PRESENCE OF CONGESTIVE HEART FAILURE	DIFFUSE HEAVING PRECORDIAL IMPULSE	PULSATION BETWEEN STERNUM AND APEX	DISTANT FIRST HEART SOUND	FIXATION OF APEX ON PERCUSSION IN LATERAL DECUBITUS	TENDERNESS OVER APEX	DISPROPORTION BETWEEN FORCE OF APEX IMPULSE AND INTENSITY OF HEART SOUND	CARDIAC ENLARGEMENT	PRESENCE OR ABSENCE OF HYPERTENSION		DIFFUSE ECCENTRICALLY DILATED CARDIAC APEX	CIRCUMSCRIBED OVAL OR ANGULAR BULGING OF LEFT VENTRICULAR BORDER	DIMINISHED SYSTOLIC CONTRACTION OF ANEURYSMAL ZONE	PRESENCE OF PLEUROPERICARDIAL ADHESIONS	CALCIFICATION OF WALLS OF THE SAC	BISSECTOR OF LEFT VENTRICLE	
9	M	43	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	3.8	
10	M	55	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	3.2	
11	M	74	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	3.4	
12	M	51	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	3.6	
13	M	47	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	2.0	
14	M	55	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	2.8	
15	M	47	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	2.0	
16	M	70	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	2.2	

*Bundle branch block.

It must be understood, however, that the absence of any one or even all of these signs does not necessarily eliminate the possibility of cardiac aneurysm. It may be concluded from the above evidence that in any given case of cardiac aneurysm there will be sufficient clinical features to suggest the diagnosis. The roentgenographic examination will confirm or contradict this impression.

CASE REPORTS

The following four cases illustrate the two types of cardiac aneurysm. Cases 1 and 9 are of the diffuse and eccentrically dilated type. Cases 2 and 10 are of the circumscribed type. In the first and second cases, taken from Table I, the diagnosis was confirmed by necropsy.



A.

B.

Fig. 2.—A, Case 1. Teleoroentgenogram showing enlargement of the heart to the left, with blunting of the apex. Typical of diffuse cardiac aneurysm. B, Case 1. Right anterior oblique roentgenogram, revealing a diffuse bulge of the left ventricular border with typical angulation. Presence of aneurysm confirmed by necropsy.

CASE 1.—R. M., a 37-year-old colored man, had been admitted to Bellevue Hospital seven times with congestive heart failure. On his first admission (Nov. 1, 1933), patient complained of substernal pain, shortness of breath, edema of both ankles, and swelling of the abdomen. Physical examination revealed a markedly enlarged heart with a diffuse precordial pulsation and a systolic murmur over apex and base. Normal sinus rhythm was present. The blood pressure was 124/96. The edge of the liver was tender and the liver was pulsating. During his stay in hospital the patient developed recurrent right-sided hydrothorax with expectoration of bloodtinged sputum. After each admission the patient improved with bed rest, digitalis, and salyrgan injections, and was discharged. At short intervals, however, increased dyspnea recurred with mild congestive failure, necessitating his readmittance to hospital. He was admitted to the hospital four times for pulmonary infarctions with expectoration of blood. The electrocardiogram revealed normal sinus rhythm, myocardial changes associated with coronary artery disease, and low voltage.

Roentgenologic examination of the heart (June 8, 1936) revealed a diffuse rounding of the left ventricle, with blunting of the apex. The roentgenogram taken in the right oblique position showed an aneurysmal bulge on the anterior heart border, with typical angulation of the left ventricular contour (Fig. 2*A* and *B*). The left auricular appendage was accentuated, the left auricle was enlarged, and the esophagus was displaced. There were fibrosis and congestion of both lung fields with obliteration of the cardiophrenic angle. Fluoroscopy showed pleuropericardial adhesions about the apex and over the right diaphragmatic dome.

Necropsy, performed Feb. 13, 1938, showed a large aneurysmal sac projecting through the anterior wall of the left ventricle, lined by a partially organized clot containing calcium. The myocardium in the apical region showed thinning and marked scarring. The wall of the sac and its overlying tissue covered an area about 3 by 1.5 cm. The anterior descending branch of the left coronary artery was completely occluded and calcified. The right coronary artery showed less thickening than the left, and no occlusion was found.

There was an adherent pleurisy of the right and left lower lobes, with infarction of the right middle lobe. A healed splenic infarct, multiple healed kidney infarcts, and cardiac cirrhosis of the liver were also found.



Fig. 3.—Case 2. A circumscribed cardiac aneurysm of the left apex. Presence of aneurysm confirmed by necropsy.

CASE 2.—M. W., a 67-year-old woman, first began to notice shortness of breath and weakness in March, 1933, followed by swelling of the feet and ankles. Physical examination on admission revealed an enlarged heart. The point of maximal impulse was in the fifth intercostal space 12 cm. from the midsternal line. The heart sounds at the apex were distant; normal sinus rhythm was present. The aortic second sound was louder than the pulmonic second. The blood pressure was 128/90. There was marked thickening of the peripheral arteries. The liver was just palpable and was tender. There was slight pretibial edema. The patient grew progressively worse and died Nov. 1, 1933.

The electrocardiogram showed normal sinus rhythm and marked left ventricular preponderance; there were no changes suggestive of myocardial damage. Roentgenologic examination showed considerable enlargement of the heart to the left, with a small, circumscribed outward bulging of the apex. This would suggest a circumscribed cardiac aneurysm of the left side of the apex (Fig. 3).

Necropsy revealed an old myocardial infarction with a small circumscribed aneurysm of the apex of the left ventricle. The anterior descending branch of the left coronary artery was occluded by an organized and partially calcified thrombus. The myocardium was hypertrophied and reddish brown in color, except for an area, 8 cm. in diameter, in the interventricular septum. There the myocardium was practically replaced by fibrous tissue, and the thickness of the wall was only about 4 mm. This area bulged into the right ventricle. The endocardium over this area was smooth and thickened. No thrombus formation was seen.

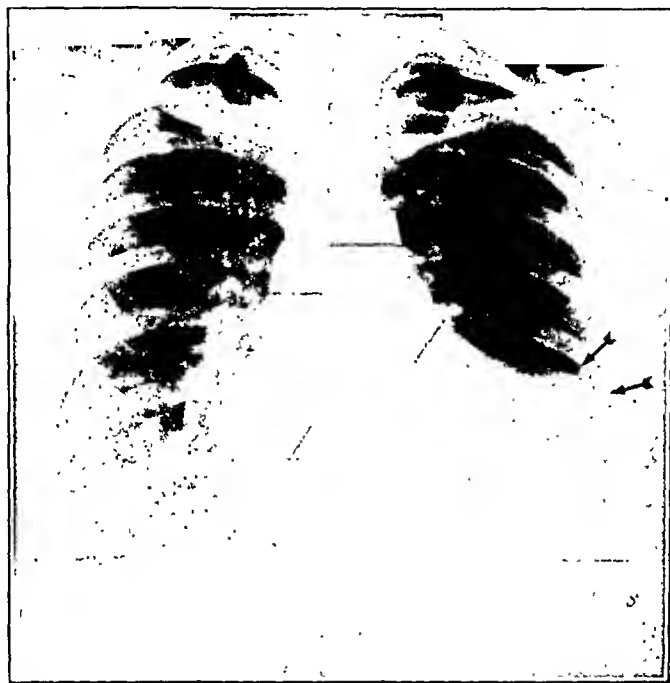


Fig. 4.—Case 9. Teleoroentgenogram showing a marked bulge of the outer portion of the left ventricle, with sharp angulation of the left border, giving the heart a rectangular appearance.

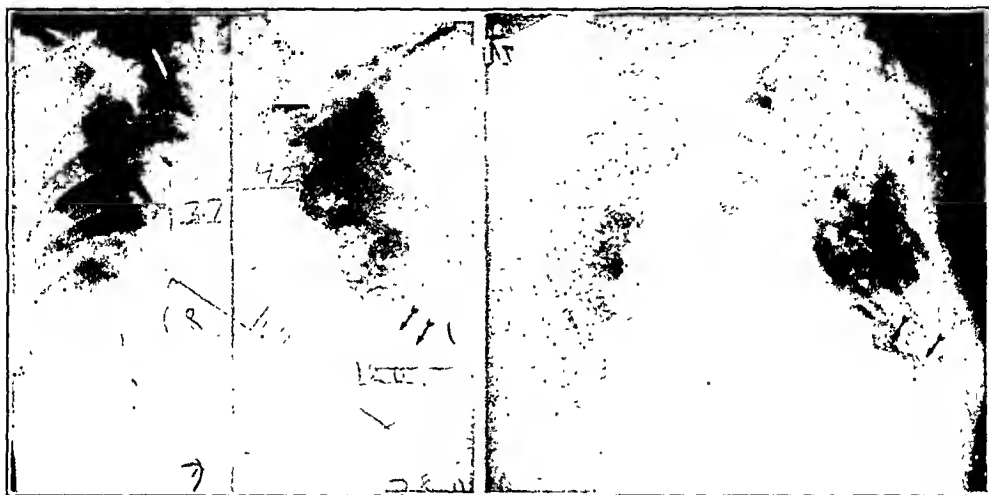
CASE 9.—L. H., a 43-year-old woman, was admitted to Bellevue Hospital three times. She had diabetes mellitus, but on her third admission (Nov. 25, 1934) she complained of a prolonged attack of severe pain across the middle of the chest, radiating to both arms.

Physical examination revealed that the heart was markedly enlarged to the left, with a diffuse precordial pulsation extending to the midaxillary line in the fifth intercostal space. In addition to the apical impulse in that space, there was a sharply localized impulse in the fourth intercostal space 14 cm. from the mid-sternal line. The first heart sound was muffled and had lost its muscular quality. There were a few moist râles in both bases, and tenderness over the liver. The electrocardiogram revealed normal sinus rhythm with left bundle branch block.

Roentgenologic examination disclosed gross enlargement of the heart to the left, mainly of the left ventricle, with sharp angulation of the left border, giving the heart a rectangular appearance. The maximum transverse diameter was 15.1 cm., the total length 16.5, the broad diameter 11.5, and the width of the pulmonary fields 25 cm. (Fig. 4).

CASE 10.—E. T., a 51-year-old man, was admitted to Bellevue Hospital Aug. 22, 1938. There was a history of severe substernal pain radiating to the left arm lasting several hours. This attack had occurred four months prior to the patient's admission to hospital. The attack was followed by gradual swelling of the feet and shortness of breath.

Physical examination on admission revealed an orthopneic, dyspneic, obese man, acutely ill. The heart was markedly enlarged. There was a feeble apex beat in the fifth intercostal space at the anterior axillary line. Fairly well-localized pain was present over this area; the heart sounds were muffled and distant, with a suggestion of gallop rhythm. Normal sinus rhythm was present, with an occasional extrasystole. The blood pressure was 90/60. Subcrepitant râles were heard over both lower lobes. The liver was four fingerbreadths below the costal margin, and there was slight pretibial edema. The electrocardiogram revealed inversion of T_1 and T_2 , suggesting anterior wall infarction.



A.

B.

Fig. 5.—A, Case 10. Teleoroentgenogram showing enlargement of the heart to the left, with a diffuse cardiac aneurysm (note B). B, Left oblique roentgenogram, showing heart seen in A. Note deep groove, and ledging of the midportion of the left ventricular border.

Roentgenologic examination revealed gross enlargement of the heart and blunting of the apex. There was congestion of both lung fields with prominence of the aortic knob. In the left oblique view there was marked ledging of the middle left ventricular border, as seen in Fig. 5. Fluoroscopic examination disclosed an enlarged heart with rounded apex and diminished amplitude of the pulsation of the left ventricle. A marked wedge-shaped indentation in the middle of the left cardiac border was observed on rotating the patient to the left oblique position (Fig. 5 A and B).

SUMMARY

1. The clinical and radiologic features of sixteen cases of cardiac aneurysm are described, in eight of which the diagnosis was confirmed by necropsy.

2. The necropsy observations have been correlated with the radiologic findings; the most constant of the radiologic signs were used as diagnostic criteria.

3. The significant clinical features are shown to be: a history of coronary thrombosis with congestive failure; cardiac enlargement; weak

first heart sound; and a diffuse heaving precordial impulse. Disproportion between the force of the apex beat and the intensity of the heart sounds, an expansile pulsation between the apex and the sternum, and localized precordial tenderness with fixation of the apex are presented as rare, but strongly suggestive, signs.

4. Since cardiac aneurysm is merely the mechanical result of fibrous transformation of the myocardium following coronary thrombosis, radiologic evidence of its presence can be seen in changes in the size, shape, and contour of the heart.

5. There are two types of cardiac aneurysm: (1) the diffuse, eccentric dilatation of the cardiac apex, and (2) the circumscribed bulge.

6. Since cardiac aneurysm is encountered in at least 9 per cent of all cases of coronary thrombosis, constant vigilance together with a knowledge of its clinical and radiologic manifestations will increase the frequency with which the condition is diagnosed during life.

REFERENCES

1. Ziegler, E.: Lehrbuch der allgemeinen und speziellen pathologischen Anatomie und Pathogenese, Jena, 1881.
2. Cohnheim, J., and Schulthess-Rechberg: Über die Folgen der Kranzarterienverschliessung für das Herz, Virchows Arch. 85: 503, 1881.
3. Hall, D. G.: Cardiac Aneurysm, Edinburgh Med. and Surg. J. 14: 322, 1903.
4. Sternberg, M.: Das chronische partielle Herzaneurysma, Wien, 1914, Franz Deuticke.
5. Kraus, F.: Ueber die Möglichkeit der klinischen Diagnose intrakardialer Aneurysmen, Berl. klin. Wchnschr. 56: 529, 1919.
6. Sigler, L., and Schneider, J.: Diagnosis of Cardiac Aneurysm, Ann. Int. Med. 8: 1033, 1935.
7. Steel, David: The Roentgen Diagnosis of Cardiac Aneurysm, J. A. M. A. 102: 432, 1934.
8. Ball, David: Aneurysm of the Heart, AM. HEART J. 16: 203, 1938.
9. Lutenbacher, R.: Aneurysmes du ventricule gauche, Arch. d. mal. du coeur 13: 49, 1920; Les lésions organiques du coeur, Paris, 1936, Masson & Cie.
10. Harvier, P., and Caroli, J.: Sur un cas d'aneurysme de la pointe du coeur, Paris med. 2: 30, 1930.
11. Christian and Frik: Roentgenbefund bei chronischen partiellen Herzaneurysma, Klin. Wchnschr. 1: 582, 1922.
12. Libman, E.: Affections of the Coronary Arteries; Inter-State Post Graduate Assembly, p. 405, Oct. 28, 1932.
13. Levine, S. A.: Coronary Thrombosis; Its Various Clinical Features, Medicine 8: 245, 1929.
14. Parkinson, J., and Bedford, D. E.: Cardiac Aneurysm, Quart. J. Med. 7: 455, 1938.
15. Zadek, E.: Beitrag zur akuten Koronarthrombose, Deutsche med. Wchnschr. 58: 1961, 1932.
16. Boller, R., and Pape, R.: Zur Diagnose des Herzaneurysmas, Fortschr. a. d. Geb. d. Röntgenstrahlen. 45: 318, 1932.
17. Kalisch, Z.: Ueber ein radioskopisch diagnostizierten und autoptisch bestätigten Fall von partiellen Herzaneurysma, Wien. klin. Wchnschr. 40: 1078, 1927.
18. Lenk, R.: Roentgendiagnose der Koronarsklerose in vivo. Gleichzeitig ein Beitrag zur Erkennbarkeit des Herzaneurysmas im Roentgenbilde, Fortschr. a. d. Geb. d. Röntgenstrahlen. 35: 1265, 1926.
19. Jaksech-Wartenhorst, R.: Herzaneurysma, Fortschr. a. d. Geb. d. Röntgenstrahlen. 33: 563, 1925.
20. Brenner, F., and Wachner, G.: Ueber einen ungewöhnlichen Sitz eines Herzaneurysmas und seine Roentgendiagnostik, Fortschr. a. d. Geb. d. Röntgenstrahlen. 54: 243, 1936.
21. Assmann, H.: Die klinische röntgendiagnostik der inneren erkrankungen, Leipzig, 1934, F. C. W. Vogel.

THE THERMAL REFLEX VASODILATATION TEST IN PERIPHERAL VASCULAR DISEASE

GABRIEL SALAND, M.D., CHARLES KLEIN, M.D., AND
HERMAN ZURROW, M.D.
NEW YORK, N. Y.

ATTENTION has already been called to the value of a vasodilating test in the study of the peripheral vascular diseases. As early as 1883, Mitchell¹ showed that paralysis of a peripheral nerve trunk by cold is associated with hyperthermia in the anesthetic zone. In 1926, Brown² obtained vasodilatation by means of the intravenous administration of typhoid vaccine. In May, 1930, White,³ and Brill and Lawrence,⁴ at the same time, but working independently, showed that spinal anesthesia caused an increase in the surface temperature of the feet.

Scott and Morton,⁵ in June, 1930, found that general anesthesia gave the same complete obliteration of vasoconstriction. Again, in October, 1931, Scott and Morton⁶ injected the posterior tibial nerve to differentiate arterial spasm from organic obstruction.

Sir Thomas Lewis,⁷ in 1929, used heat to induce peripheral reflex vasodilatation.

In 1932, Gibbon and Landis⁸ observed that immersing the hands and forearms in warm water produced vasodilatation in the lower extremities of six normal persons, and that the temperature of the toes began to rise in fifteen minutes and rose to over 31.5° C. in all cases. In November, 1933, Landis and Gibbon⁹ studied patients with peripheral vascular disease, and found that the immersion test compared favorably with other methods of vasodilatation.

The reason for using a vasodilatation test is obvious to all workers in the field of vascular diseases. It is a known fact that arterial spasm can simulate every symptom and physical sign of organic obstruction, such as cold feet, painful extremities, claudication, absent pulsations, rubor, and pallor. It is also known that instrumental aids, such as oscillometric tracings and intra-arterial thorotrast injections, reveal only the presence or absence of obstruction, but when obstruction is demonstrated, these tests do not differentiate spasm from organic block.

In our work we followed the method of Gibbon and Landis for the following reasons: (1) it eliminated the danger of trauma to the vessels, (2) injection carried with it the risk of infection, and (3) many patients objected to an injection.

From the department of peripheral vascular diseases, Bronx Hospital, New York.
Received for publication Oct. 29, 1933.

We are reporting results on seventy-three patients who had symptoms of peripheral vascular disease. Each patient had a complete history and physical examination, urine examination, blood counts, and blood Wassermann and Kahn tests. When necessary, a chemical examination of the blood was made and electrocardiograms taken. The local examination was supplemented by recorded oseillometrie tracings at the knee and ankle, roentgenograms of the peripheral vessels and, finally, by the thermal test.

Just prior to doing the thermal test the case was classified as either one of organic, functional, or no peripheral vascular disease. However, in this report we divided our cases into two main groups, namely, Group I, cases in which the temperature of the big toe rose to 30.5° C. or over, and, Group II, cases in which the temperature of the big toe failed to rise to 30.5° C.

Technique of the Test.—We followed the technique of Gibbon and Landis.⁸ We tried to keep the room temperature as constant as possible, and avoided all drafts. The subject, whose rectal temperature was not over 100° F., was seated on a chair with the lower extremities in the horizontal position, exposed from above the knees. The readings were taken with the Taylor Dermatherm on the dorsum of the big toe at the base of the nail. Both extremities were examined. Readings were taken until the temperature of the big toe was the lowest possible at the room temperature prevailing. We tried to have the initial temperature of the big toe 26° C., or lower; this frequently necessitated an exposure of one-half hour or longer. Both forearms and hands were then immersed in water at 45° C., and readings from the big toes were taken with the dermatherm every three minutes for a period of one-half hour. At the time of immersion the patient's body was covered with wool blankets. Rectal temperatures were taken at the end of each test. Normally, a significant rise in toe temperature should occur in fifteen minutes, and at the end of thirty minutes should reach the absolute value of 30.5° C., or over.

For the sake of simplicity in following our results we have reported the findings in only one extremity, and we have selected the extremity showing the lower reading.

Rationale of the Thermal Test.—Immersion of the forearms in water at 45° C. tends to raise the temperature of the blood in those limbs. When the warmer venous blood reaches the medulla it affects the vasomotor center, inducing a reduction of vasomotor tone in an attempt to maintain constant body temperature.

Group I (A).—Cases in which the temperature did not rise to 30.5° C. (initial temperature of the big toe 26.0° C., or lower). In this group there were forty-four cases, including thirty-three of arteriosclerosis obliterans with or without ulceration, infection, or gangrene, five cases of thromboangiitis obliterans, one of scleroderma, one of thrombophlebitis with arteritis, one of vasospasm, and three in which no vascular disease was diagnosed. Forty subjects in this series failed to show an elevation of the temperature of the big toe to 30.5° C. In other words, the thermal test gave corroborative evidence of organic obstruction in forty out of forty-four cases, or 91 per cent. However, four patients who were re-

garded as having no organic obstruction also failed to show a rise to the absolute value of 30.5°C .

Group I (B).—Cases in which the temperature did not rise to 30.5°C . (initial temperature of the big toe above 26.0°C .). This group comprised eleven cases of arteriosclerosis obliterans, with or without ulceration, infection or gangrene. In no instance, in spite of the fact that the initial temperature of the big toe was over 26.0°C ., was there a rise to 30.5°C . In other words, there was 100 per cent corroboration of the presence of organic vascular disease in this series. The percentage corroboration of the test for the entire Group I was 93 per cent.

Group II (A).—Cases in which the temperature rose to 30.5°C ., or over (initial temperature of the big toe 26.0°C ., or lower). In this group there were seven cases, in all of which the diagnosis of no peripheral vascular involvement had been made. In all of these cases the temperature of the big toe rose as it would in a normal individual, a 100 per cent corroboration by the thermal test of the fact that in these cases there was no organic obstruction.

Group II (B).—Cases in which the temperature rose to 30.5°C ., or over (initial temperature of the big toe above 26.0°C .). In this group there were eleven cases, including two of arteriosclerosis obliterans, one of Raynaud's disease, and eight in which no peripheral vascular disease was diagnosed. The patient with Raynaud's disease had no involvement of the lower extremities, and for the purpose of this article may be grouped with the nine normal subjects. All eleven subjects showed a rise in the temperature of the big toe to 30.5°C . In this group, therefore, the thermal test corroborated the clinical findings in 82 per cent of the cases.

TABLE I
SUMMARY OF THERMAL RESPONSE

DIAGNOSIS	TOTAL NO.	SURFACE TEMPERATURE OF BIG TOE		PER CENT CORROBORA- TION OF DIAGNOSIS BY THERMAL TEST
		ROSE TO 30.5°C .	FAILED TO RISE TO 30.5°C .	
Organic occlusive arterial disease	53	2	51	96
No peripheral vascular disease	20	16	4	80

DISCUSSION

We have studied seventy-three patients who were sent to our clinic for diagnostic and therapeutic purposes. We did a vasodilatation test in each case in addition to using other known methods of proving the presence or absence of organic obstruction. We have shown that in cases in which there was no evidence of vascular disease the thermal test was normal in 80 per cent, and that in those in which a diagnosis of organic obstruction had been made the thermal test showed that the surface

temperature of the big toe failed to rise to 30.5° C. in 96 per cent of the cases.

In two cases in which a clinical diagnosis of arteriosclerosis obliterans was made, the response to the thermal test was normal. One must assume in such cases that either there is an element of spasm, and that this spasm is relaxed by vasodilatation, or that there exists a sufficient collateral blood supply to allow enough blood to reach the extremity and warm it. If the latter should be true, then it is rational to assume that this test can be used to measure the effect of any kind of therapy used in peripheral vascular disease.

CONCLUSION

The thermal reflex vasodilatation test is a safe and simple method to differentiate organic from nonorganic obstruction of the peripheral arterial system, and also to determine whether or not the blood supply to a limb is sufficient.

REFERENCES

1. Mitchell, S. W.: Cases of Lesions of Peripheral Nerve-Trunks, With Commentaries, *Am. J. M. Sc.* 85: 17, 1883.
2. Brown, G. E.: The Treatment of Peripheral Vascular Disturbance of the Extremities, *J. A. M. A.* 87: 379, 1926.
3. White, J. C.: Diagnostic Blocking of Sympathetic Nerves to Extremities with Procaine, *J. A. M. A.* 94: 1382, 1930.
4. Brill, S., and Lawrence, L. B.: Changes in Temperature of the Lower Extremities Following the Induction of Spinal Anesthesia, *Proc. Soc. Exper. Biol. & Med.* 27: 728, 1930.
5. Scott, W. J. M., and Morton, J. J.: Obliteration of Vasoconstrictor Gradient in the Extremities Under Nitrous Oxide-Oxygen, Ether and Tribrom-Ethyl Alcohol Anesthesias, *Proc. Soc. Exper. Biol. & Med.* 27: 945, 1930.
6. Scott, W. J. M., and Morton, J. J.: Differentiation of Peripheral Arterial Spasm and Occlusion in Ambulatory Patients, *J. A. M. A.* 97: 1212, 1931.
7. Lewis, T.: Experiments Relating to Peripheral Mechanism Involved in Spasmodic Arrest of Circulation in the Fingers, a Variety of Raynaud's Disease, *Heart* 15: 7, 1929.
8. Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in the Lower Extremities in Response to Immersing the Forearms in Warm Water, *J. Clin. Investigation* 11: 1019, 1932.
9. Landis, E. M., and Gibbon, J. H., Jr.: A Simple Method of Producing Vasodilatation in the Lower Extremities, *Arch. Int. Med.* 52: 785, 1933.

THE INTERPRETATION OF THE U WAVE OF THE ELECTROCARDIOGRAM*

L. H. NAHUM, M.D., AND H. E. HOFF, M.D.†
NEW HAVEN, CONN.

THE U wave was first observed by Einthoven in the electrocardiogram of a patient with myocardial disease and was attributed to the abnormal duration of ventricular systole in a damaged heart.¹ Subsequently, Einthoven found the U wave in electrocardiograms of normal subjects, and concluded that the wave indicated persistence of contraction in some fibers during early diastole.² Lewis and Gilder³ recognized this summit in thirty-two cases out of forty-nine in Lead I, in forty-four out of forty-nine in Lead II, and in fourteen out of thirty in Lead III. By means of simultaneous electrocardiographic and carotid pulse curves, they calculated that the U wave occurred almost, if not entirely, after the closure of the semilunar valves. Soon afterward, Hering⁴ suggested that the U wave may be caused by electrical activity in the great arteries.

Since then the possibility that the U wave may represent a phase of electrical activity of the ventricle has been disregarded, and the concept that electrical and mechanical events in the ventricle terminate more or less simultaneously at the end of the T wave has developed. Recently, however, the work of Erlanger and Gasser⁵ on nerve has revealed the existence of after-potentials whose duration far exceeds the period of excitation accompanying propagation of the impulse; such potentials are associated with the various phases of the recovery process. Factors which influence metabolism and affect recovery are found to have a profound influence on these after-potentials. A phase of recovery particularly influenced in this manner is the supernormal period which follows the relative refractory phase and is associated with the negative after-potential.

The supernormal period has in the past been found infrequently in the frog's ventricle,^{6, 7} the conduction system,^{8, 9} and the pacemaker.¹⁰ In a previous communication we have demonstrated that it is invariably present in the ventricle of the cat under amytal anesthesia, and have found that when a U wave is present the supernormal period coincides with it.¹¹ We concluded that the U wave is to be considered a part of the ventricular complex, representing the location of the supernormal period. The present study was undertaken to determine whether the U wave and

*Aided by a grant from the Fluid Research Funds, Yale University School of Medicine. We are indebted to the Department of Cardiology, Grace Hospital, New Haven, for part of the clinical material presented here.

†Laboratory of Physiology, Yale University School of Medicine, New Haven.

Received for publication Oct. 31, 1938.

the supernormal phase coincide in other mammals, and to ascertain how this interpretation of the U wave may contribute to our understanding of the ventricular electrocardiogram in man.

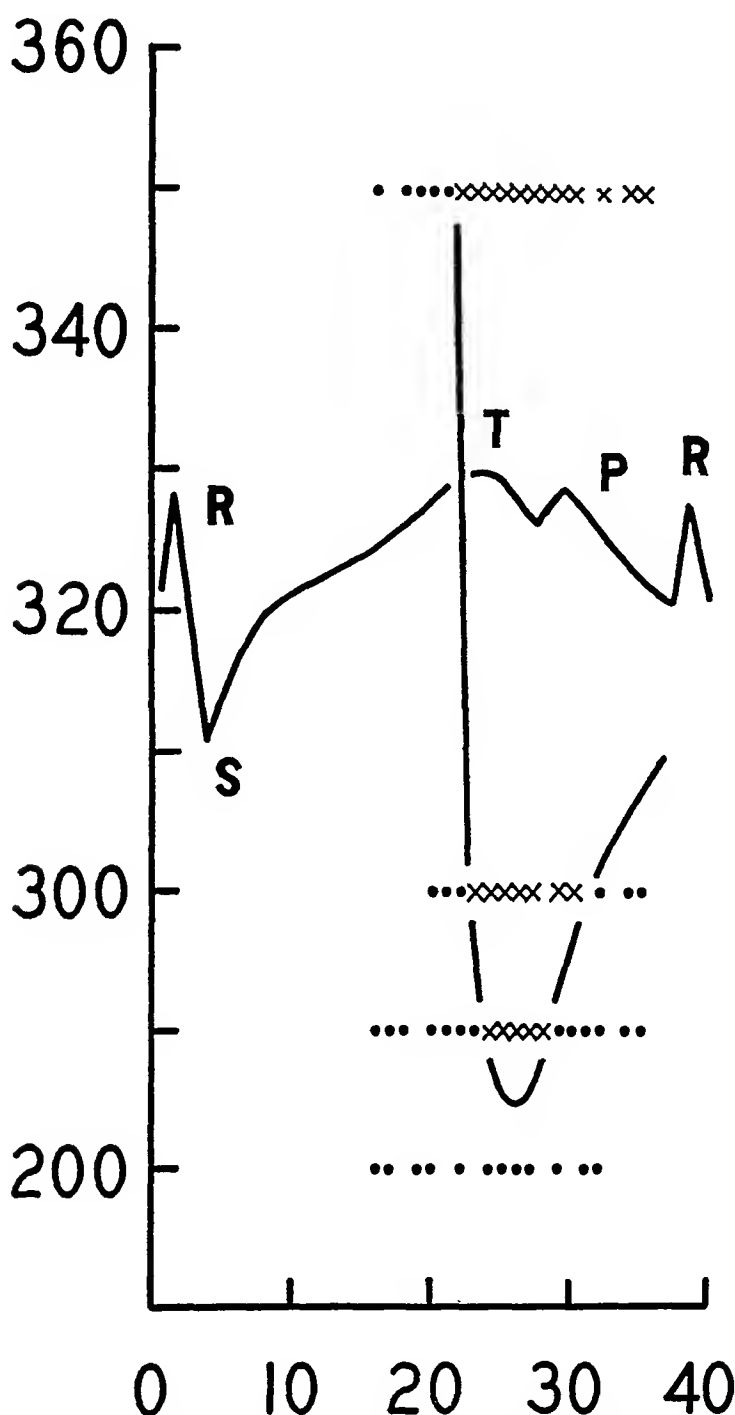


Fig. 1.—Chimpanzee Becky, 32 kg. Sodium amytal anesthesia (60 mg. per kg.). Heart exposed through sternum and anterior mediastinum without opening pleural cavities. Point stimulated on anterior surface of left ventricle. Ordinates, peak voltage of induction shocks. Abscissae, time in hundredths of a second. Crosses represent shocks which evoked extrasystoles, and dots ineffective shocks. From 0.22 to 0.30 after the onset of R, shocks are effective at strengths which later in the cycle fail to evoke a response. This is the supernormal period. A scale drawing of a single electrocardiographic complex from Lead II shows that the supernormal phase occurs here during the descending portion of T.

EXPERIMENTAL STUDIES

The recovery cycle of the hearts of six dogs and one adult chimpanzee was studied by the method previously described.¹¹ The heart was exposed and the pericardium sewed to the chest wall in such a manner that the pleural cavities were closed, and the animal could breathe. A silver hook was inserted into the epicardium over the ventricle and paired with an anal electrode, permitting induction shocks to be delivered to the heart. By varying the strength of these shocks, the excitability of the heart was determined throughout the cycle. The usual absolute refractory period was determined, when no stimulus of whatever strength could evoke an extrasystole. This was followed by the relative refractory period, during which shocks were able to elicit a response provided they were of greater intensity than those which were effective during late diastole. Subsequent to this the excitability of the heart increased, so that a shock too weak to evoke a response later in diastole now produced an extrasystole. This period is recognized as the supernormal period, and lasted from 0.10 to 0.15 second. It appeared in all animals anesthetized with sodium amytal, but was not detectable when morphine was employed as the analgesic.

In the chimpanzee (Fig. 1) and in one dog the supernormal period was found on the down stroke of the T wave, and a U wave was not detected. In two other dogs U waves were seen, and in these animals the supernormal period fell on the U wave (Fig. 2). In one of these experiments the supernormal period was inconstant, appearing and disappearing within a few beats, but without any recognizable relation to respiration. These experiments confirm the observations on cats, and establish the existence of a supernormal phase in the ventricles of larger mammals, including primates. They demonstrate the relation of the supernormal period to the descending limb of the T wave in rapidly beating hearts when there is no U wave, and to the U wave when it is present.

THE U WAVE IN MAN

The Presence of the U Wave.—Two conditions are essential for detection of the U wave: (1) a sufficiently slow heart rate, and (2) the absence of auricular fibrillation. Since the U wave follows T, and precedes P, the diastolic interval must be long enough to prevent obscuring of the U by the oncoming P. In man the maximum rate which permits recognition of U is between 90 and 100. This is well illustrated by Fig. 3B, in which, with sinus arrhythmia and a rate ranging from 105 to 75, the U wave is shown gradually emerging from beneath the P wave. In children, a conspicuous U wave may be seen with considerably higher heart rates (Fig. 3A). While U waves can at times be seen when the auricles are fibrillating and the ventricular rate is slow, the irregular auricular waves usually make it difficult, if not impossible, to identify them.

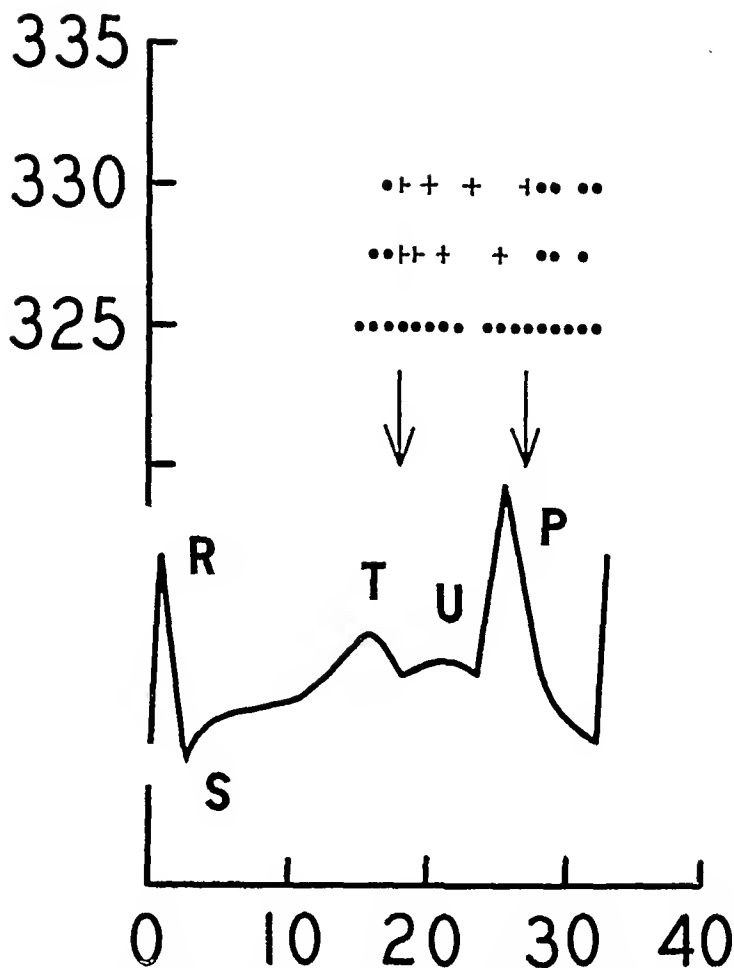


Fig. 2.—Dog, 20 kg. Sodium amytal anesthesia. Chart constructed as in Fig. 1. The arrows indicate the supernormal period, which here falls on the U wave.

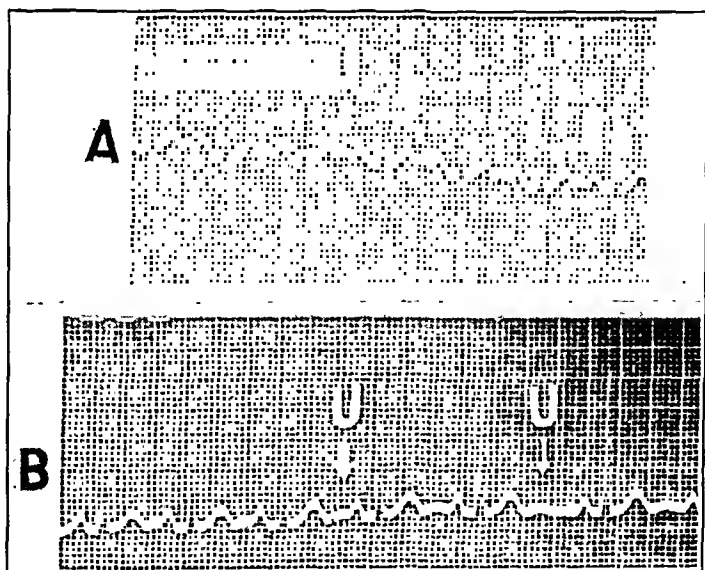


Fig. 3.—A, Lead IV R from a 15-year-old boy, showing a U wave, with a heart rate of 150; B, Lead IV R showing U wave emerging from beneath P as the heart slows.

Of 151 electrocardiograms without manifest evidence of abnormality, the U wave was recognized distinctly in 10 per cent in Lead I, 10 per cent in Lead II, 6 per cent in Lead III, and 75 per cent in Lead IV R. Only those U waves which had an amplitude of more than 0.25 mm. and a duration which could be measured definitely were recognized. This

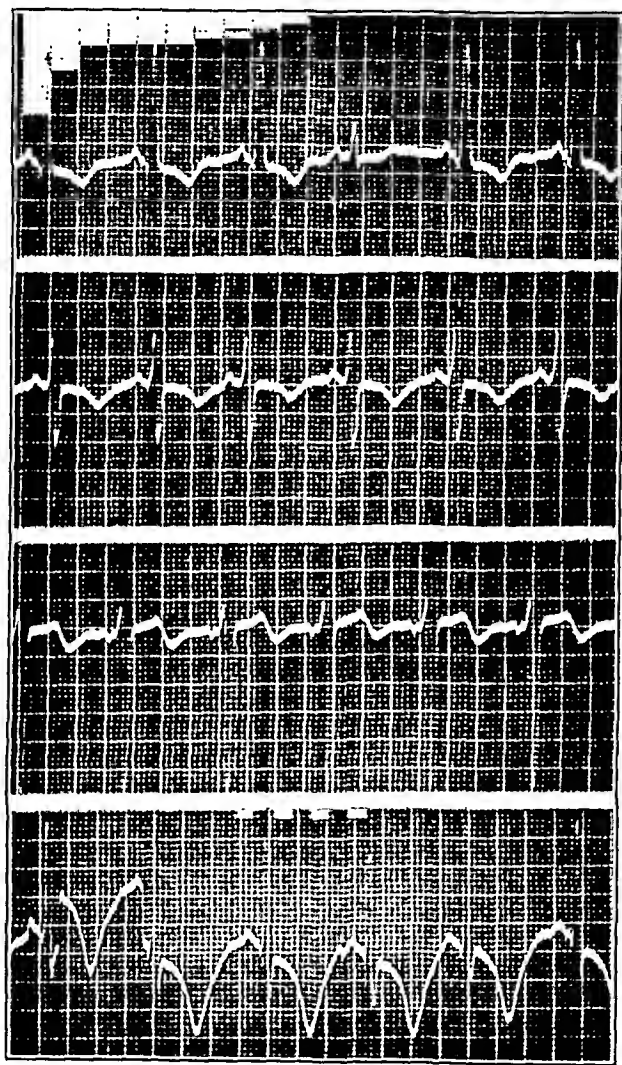


Fig. 4.—Leads I, II, III, and IV R, reading from top to bottom, showing wide T waves in a patient with coronary artery disease.

may account for the lower frequency of U waves in the conventional leads in this series than in that of Lewis and Gilder. It does, however, render all the more striking the higher incidence of U waves in Lead IV R.

By contrast, in the electrocardiograms of ninety-three patients showing evidence of myocardial disease, the incidence of the U wave in Lead IV was only 40 per cent, and 4.4 per cent in Lead I. Lead II, with

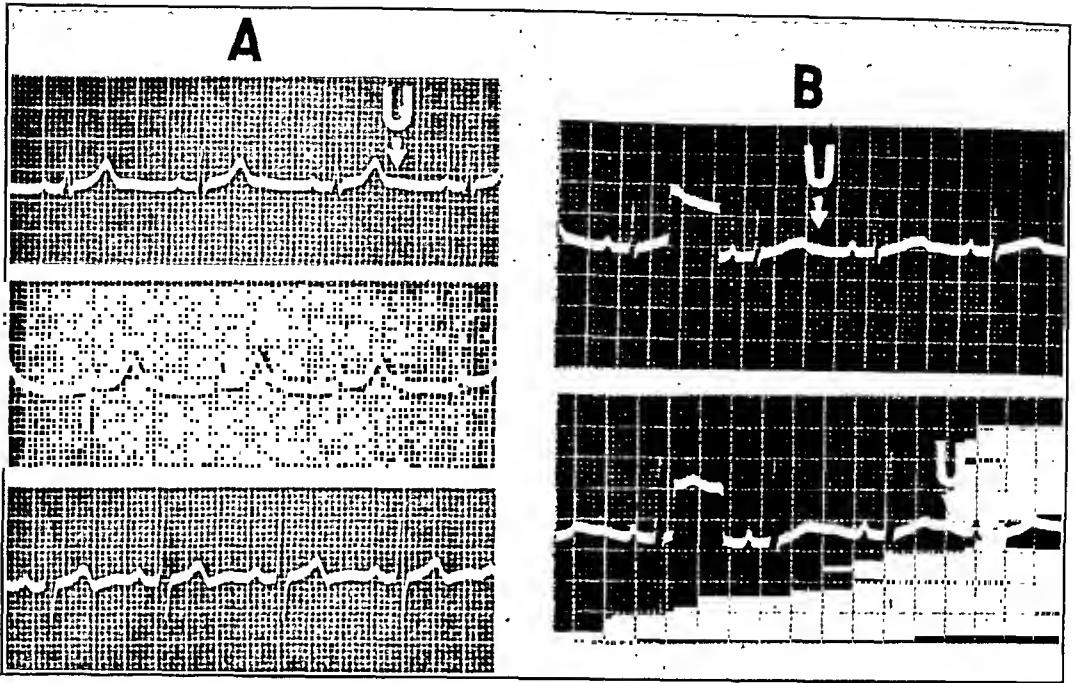


Fig. 5.—A, Leads II, III, and IV R, showing U on the terminal portion of T. B, Leads II and IV R which also show a confluence of T and U.

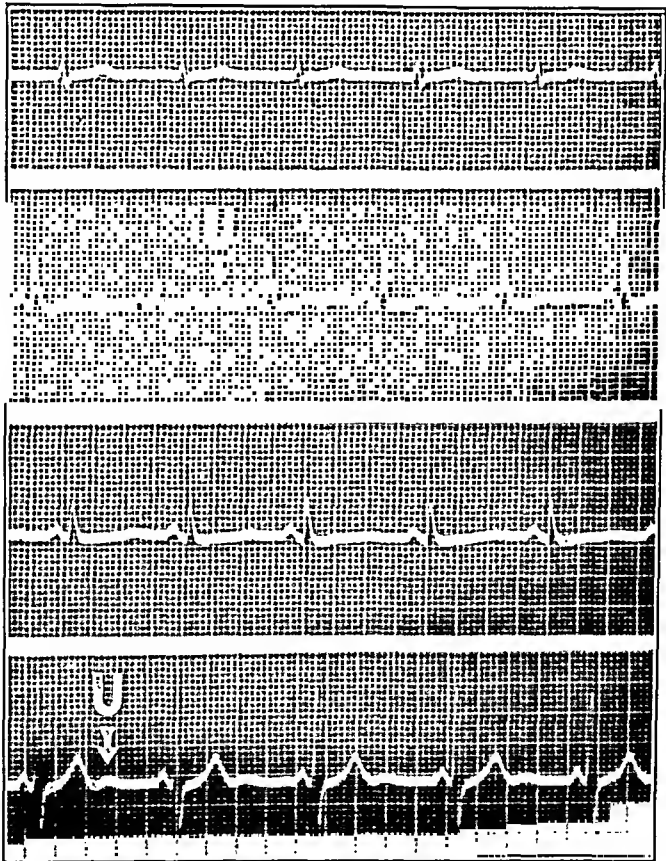


Fig. 6.—Records from Leads I, II, III, and IV R, showing fusion of T and U in Lead III.

10.1 per cent, and Lead III, with 7.4 per cent, were practically the same as normal. At least one reason for this is apparent in some records. Fig. 4 is taken from a patient with hypertensive heart disease and cardiac infarction, and shows a remarkable widening of the S-T interval, extending in Lead IV as far as the onset of P. In such a record a U wave would of course be entirely obscured. An earlier stage in this same process, with incomplete fusion of U and T, is shown in Fig. 5A, which is the record of a patient with coronary thrombosis. An even earlier stage is found in Fig. 5B; in this case the only diagnosis made by the electrocardiogram was right axis deviation, while the clinical diagnosis was active rheumatic heart disease. Thus far, such a fusion of T and U has been found only in records of patients with damaged hearts. Occasionally in such hearts the fusion may be marked in one lead, and not exist in the others (Fig. 6, Lead III).

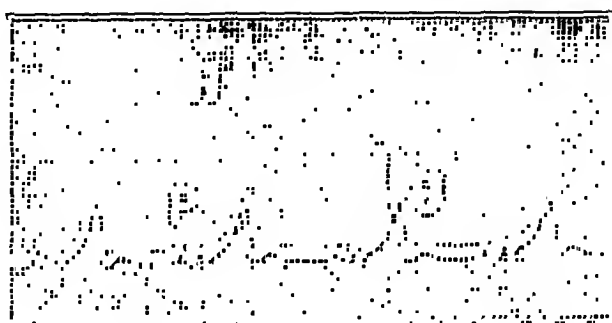


Fig. 7.—The most pronounced U wave found in a normal subject, Lead IV R.

Amplitude and Direction.—The U wave in normal subjects appears as a low summit never more than 1.50 mm. high, but more often from 0.25 to 0.75 mm. It usually begins 0.04 second beyond the end of T, and continues for 0.16 to 0.24 second, with an average duration of 0.20 second (Fig. 7). While in the normal subjects the U wave was invariably upright, this was not the case in the patients with damaged hearts. As mentioned above, only 40 per cent of the patients with damaged hearts showed any kind of a U wave in Lead IV R. Of these, thirty-six in number, twenty-four were found to exhibit an inverted U wave. The inverted U wave was thus found only when heart disease was present, and at times was the only electrocardiographic evidence of damage. Two examples of this are shown in Fig. 8. In A, B, and C are shown Leads I, II, and IV R from a patient with hypertension, arteriosclerosis, and coronary sclerosis; the inverted U is practically the only electrocardiographic evidence. In D is shown Lead IV R of a patient with hypertensive and coronary heart disease with congestive failure, and again the inverted U is the only abnormal electrocardiographic sign. Fig. 9, A and B, shows Leads III and IV from a patient with bundle branch block, and shows a negative T and a negative U in

Lead III, but positive T and U in Lead IV R. Inversion of the U wave was not associated with any one specific disease, but with a variety. The most common were coronary artery disease, with or without thrombosis, rheumatic valvular disease, hypertensive heart disease, and pulmonary heart disease.

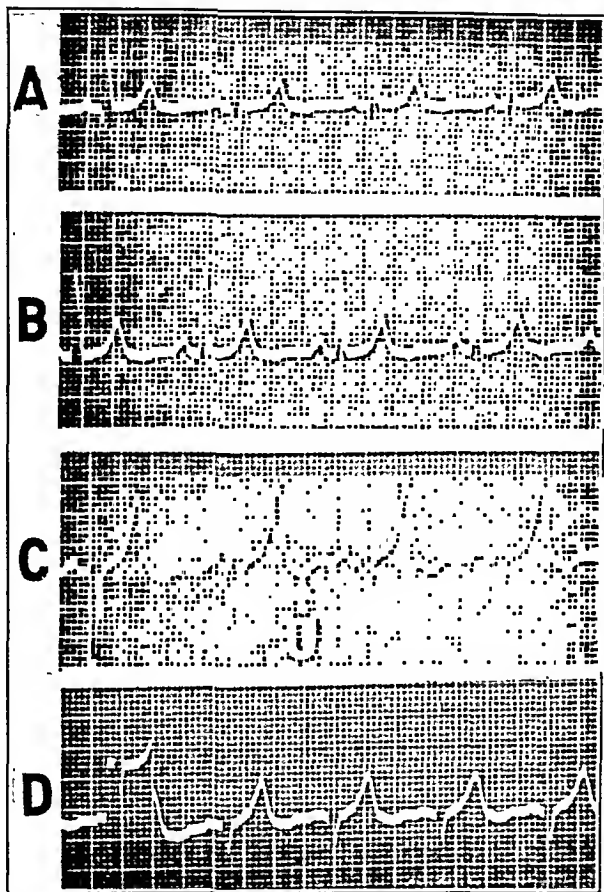


Fig. 8.—A, B, and C are Leads I, II, and IV R from a patient with arteriosclerosis, coronary sclerosis, and hypertension, showing negative U waves with positive T waves. D is Lead IV R from another patient with hypertensive heart disease, showing negative U waves.

Certain circumstances alter the amplitude of U. Following ventricular extrasystoles the U wave may become much more pronounced, as in Fig. 9C, but may also disappear, as in Fig. 10. The U wave may be pronounced in cases of bundle branch block, as shown in Fig. 9, A and B, though this is again not invariably so.

The U Wave and Extrasystoles.—In seven of the records included in this study a bigeminal rhythm was found. In all these the ectopic beat fell either on a clearly marked U wave (Fig. 10, A and B) or in that part of the cycle in which the U wave is found (e.g., within 0.024 second after the termination of T). Study of the position of the ectopic beat in published records of bigeminy confirms this completely. It was noted that while an exact coupling was often found, at other times the onset of the premature beat varied within limits of 0.06 to 0.08 second.

Isolated extrasystoles of ventricular origin were found to occupy three parts of the cycle, depending on the rate of the heart (Fig. 11). By far the greatest number, occurring in hearts beating at intervals of 0.60 to 0.80 second, fell either on the U wave (Fig. 10, *A* and *B*) or within 0.24 second after the end of T. With more rapid rates extrasystoles were less frequent, but in one record in which extrasystoles were found they appeared on the descending limb of T (Fig. 10, *C* and

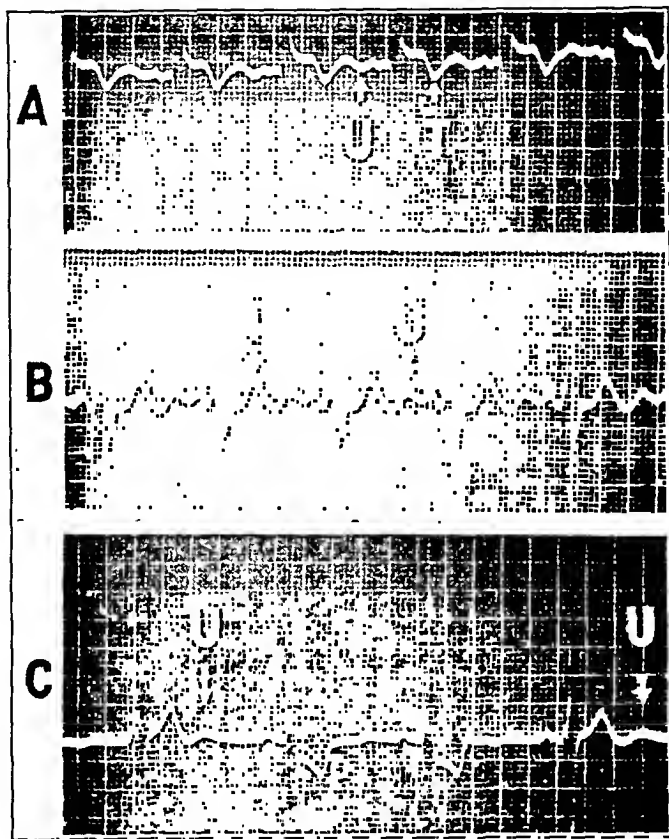


Fig. 9.—*A* and *B* are Leads II and IV R, and show the pronounced U wave in intraventricular block and a negative U. *C* is Lead IV R, showing the pronounced U waves following ventricular extrasystoles.

D). It should be recalled that in cats, dogs, monkeys, and the chimpanzee, rapid rates revealed that the supernormal period lay on the descending slope of T. In slowly beating hearts isolated extrasystoles may fall late in the cycle (Fig. 11), in addition to falling upon the U wave. The slowness of rate and the lateness of the extrasystoles suggest that these may be caused by the well-known phenomenon of ventricular escape. Thus two types of extrasystoles may be discerned, the first of the escape type, not related to the U wave, and the rest, including the coupled extrasystoles in bigeminy, which fall in the part of the cycle occupied by the U wave.

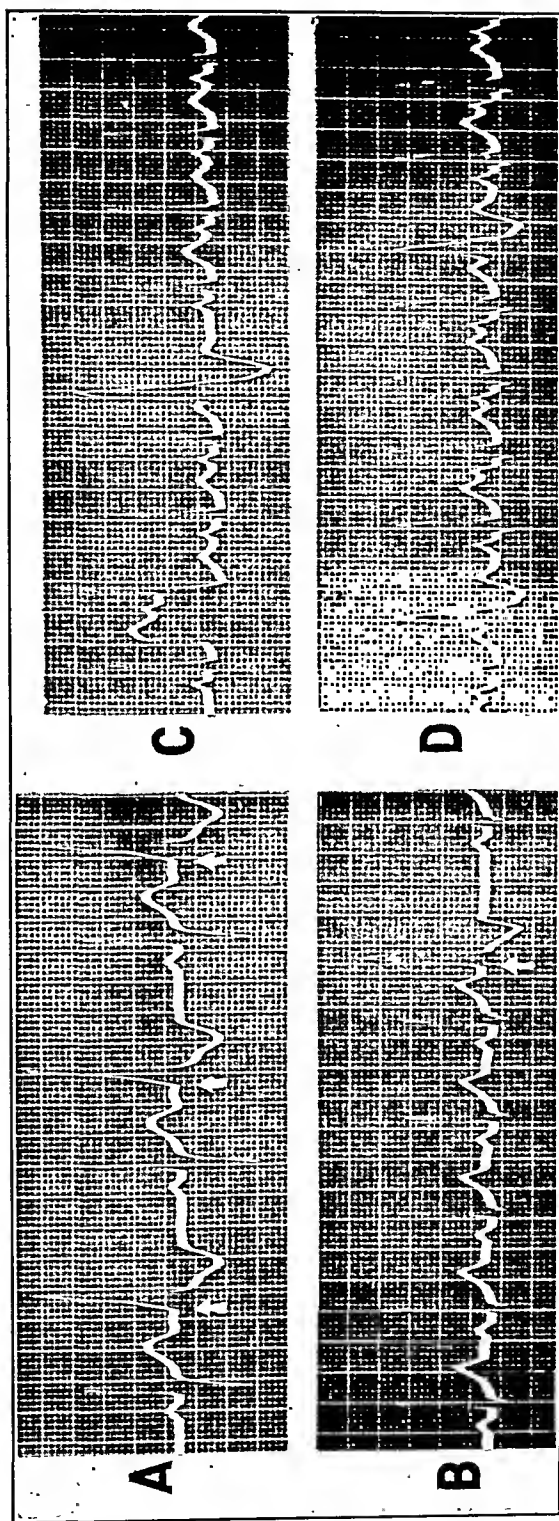


Fig. 10.—A and B are Lead IV R from two subjects, showing ventricular extrasystoles falling on the U waves. C and D are Lead IV R from two other subjects, showing ventricular extrasystoles falling on the descending limb of the T wave in hearts beating more rapidly. Compare these with Figs. 1 and 2.

Experimentally, this period is found to be the time of supernormal excitability, when this phenomenon exists. The fact that the majority of ventricular extrasystoles occur at this same time may be more than a mere coincidence, and may indicate the existence of some correlation between the supernormal period and certain extrasystoles.

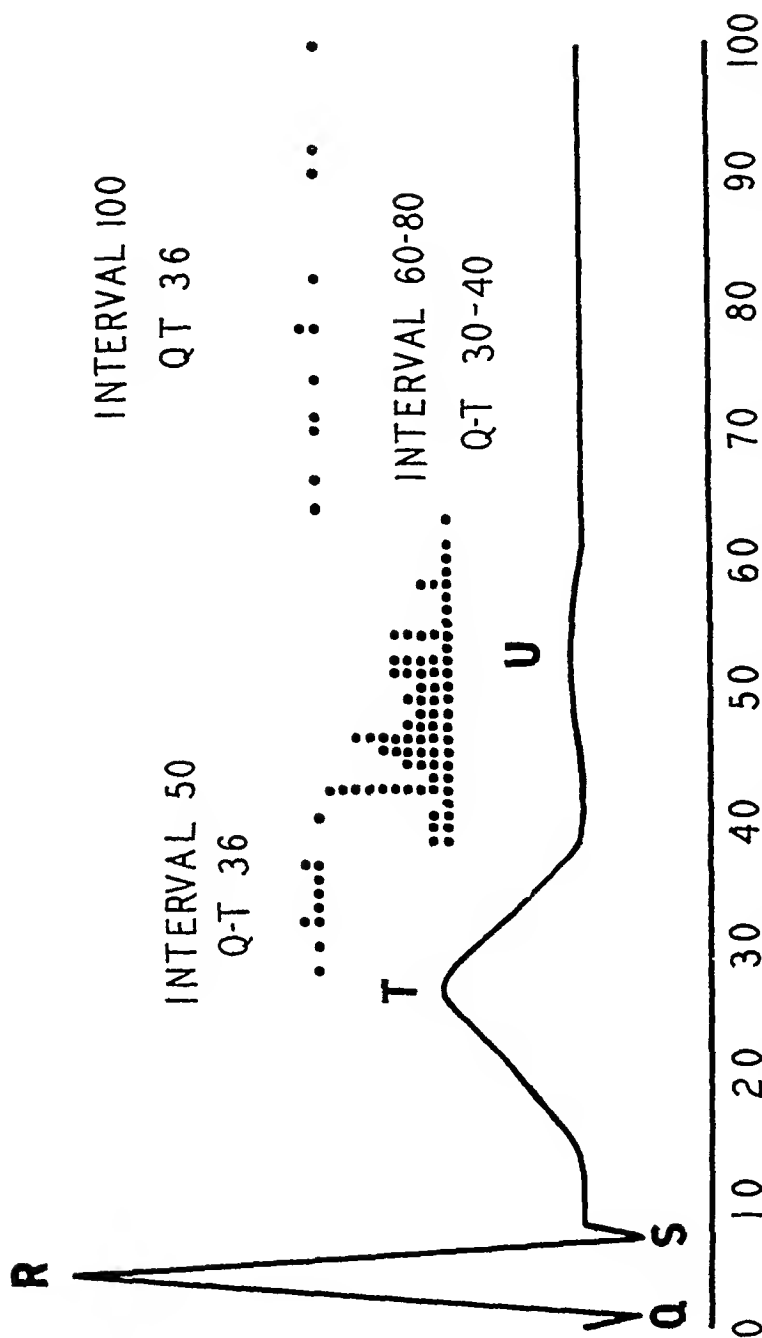


Fig. 11.—A graph indicating the part of the cycle in which ventricular extrasystoles fall. Each dot represents a single extrasystole taken from records studied in this report. Abscissae represent time in hundredths of a second.

DISCUSSION

Experimental evidence furnished elsewhere and confirmed and extended in this report proves that beyond the T wave are to be found electrical events (*the U wave*) associated with the recovery phase of the previous systole, and that the end of the T wave does not mark the end of electrical systole. This period of continuing electrical activity is the U wave, and is the site of the supernormal phase when it is present. The existence of a U wave in the human electrocardiogram in the same

part of the cycle as in other animals indicates that in man also the U wave is a part of the ventricular complex, and marks that part of the cycle where a supernormal phase can be expected.

The basic investigations of Erlanger and Gasser on the recovery cycle in nerve have demonstrated that the supernormal period is associated with the negative after-potential. This after-potential and the supernormal period associated with it have been shown to be particularly variable, and are capable of being increased by acid, asphyxia, and certain drugs such as veratrine, and decreased by factors which improve the metabolic condition. Although the U wave thus represents the negative after-potential, it must be remembered that it is in reality the summation of events in individual fibers, and therefore is influenced by physical factors of position and distribution of muscle mass as well as by factors that change the after-potentials themselves. This is clearly shown by its variation in different leads. This makes it difficult to draw conclusions concerning the supernormal period and the negative after-potentials from the state of the U wave. Nevertheless, since the experimental evidence clearly shows that changes in the metabolic condition of the tissue are reflected in changes in the negative after-potential, it might be expected that the U-wave changes would be found in some damaged hearts. This, in fact, has been noticed in the analysis of records from ninety-three patients with diseased hearts. The U wave tends to disappear from Lead IV R, to fuse with the T wave in all leads, and to become inverted. In fact, neither a negative U wave nor a fusion of T and U was ever observed in electrocardiograms from persons with normal hearts.

The usual concept that the end of T is the end of the electrical cycle is no longer tenable. This is dramatically illustrated in Fig. 12, showing a number of electrocardiograms in which it is difficult to detect in Lead IV R the demarcation between T and U or to assign to any point in diastole the end of the ventricular complex.

Study of the extrasystoles which occurred in this group of records revealed that they fell, with few exceptions, during the part of the cycle in which a supernormal period might be expected to exist. The only exception was that when the heart was beating very slowly they might have been a manifestation of the well-known phenomenon of ventricular escape, and not at all related to a supernormal phase. Previous workers have already suggested a causal relationship between the supernormal phase and extrasystoles. Gasser noticed that nerves showing a marked supernormal phase were likely to respond to a single stimulus by prolonged repetitive discharge, during which each succeeding discharge occurred at the height of the supernormal period following the previous beat. He explained this on the basis of an internal subliminal stimulus which was incapable of initiating spontaneous activity when the tissue was at rest. When, however, the nerve was once stimulated,

the resulting supernormal phase lowered the threshold to a point where the latent internal stimulus became effective. This reasoning was applied to the Purkinje fibers of the heart by Goldenberg and Rothberger.⁹ In the heart it is known that the ventricular conduction system possesses an inherent automaticity, usually subliminal. If, however, a marked supernormal phase develops, it is possible that at this time the latent stimulus will become effective, and evoke an extrasystole.

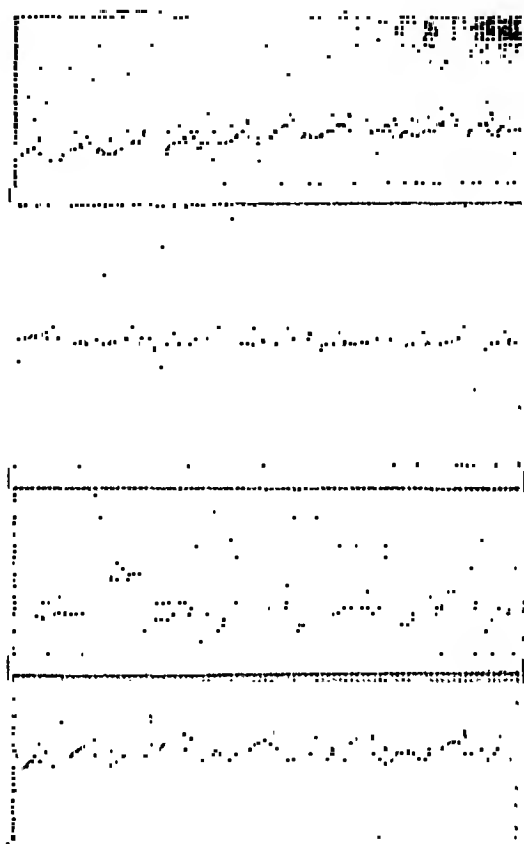


Fig. 12.—Records from Lead IV R which illustrate the difficulty occasionally encountered in determining the end of T and U.

Upon the supernormal period may thus depend the type of arrhythmia which develops. If it is not marked, the latent stimulus may be insufficient to produce a response; if it comes and goes, as it was seen to do in experiments, isolated extrasystoles would be found at various points in the period. If continually present it might produce bigeminy, or even an attack of paroxysmal tachycardia.

It is of course obvious that the intensity of the internal stimulus must play an important part. Whatever the effect of the supernormal phase, if the internal stimulus is inadequate no response may be expected. On the other hand, heightened automaticity of the conduction system may evoke discharge without the help of a supernormal phase. Ventricular

escape from vagal inhibition is an example of this, as are the ventricular rhythms in A-V block and the ventricular beats following intravenous injection of adrenaline.

SUMMARY

1. The U wave of the human electrocardiogram is a part of the ventricular complex.
2. It represents the part of the cycle in which the supernormal phase occurs.
3. It tends to disappear in some cases of heart disease.
4. Inversion of the U wave or fusion of the U wave with the T wave is found only in patients with damaged hearts.
5. The majority of ventricular extrasystoles fall on the U wave or the part of the cycle where it occurs.

REFERENCES

1. Einthoven, W.: Le télécardiogramme, *Arch. Internat. de Physiol.* 4: 132, 1906-07.
2. Einthoven, W.: The Different Forms of the Human Electrocardiogram and Their Signification, *Lancet* 1: 853, 1912.
3. Lewis, T., and Gilder, M. D. D.: The Human Electrocardiogram: A Preliminary Investigation of Young Male Adults, to Form a Basis for Pathological Study, *Phil. Trans. Roy. Soc. Lond.* 102 B: 351, 1912.
4. Hering, H. E.: Experimentelle Studien an Säugethiern über das Elektrokardiogramm, *Pflüger's Arch. f. d. ges. Physiol.* 127: 155, 1909.
5. Erlanger, J., and Gasser, H. S.: Electrical Signs of Nervous Activity, Philadelphia, 1937, Pennsylvania University Press.
6. Adrian, E. D.: The Recovery Process of Excitable Tissue. II, *J. Physiol.* 55: 193, 1921.
7. Wastl, H.: Die übernormale Phase der Erholung des Herzmuskels nach einer Systole, *Ztschr. f. Biol.* 75: 289, 1922.
8. Lewis, T., and Master, A. M.: Supernormal Recovery Phase, Illustrated by Two Clinical Cases of Heart-Block, *Heart* 11: 371, 1924.
9. Goldenberg, M., and Rothberger, C. J.: Über das Elektrogramm der spezifischen Herzmuskulatur, *Pflüger's Arch. f. d. ges. Physiol.* 237: 295, 1936.
10. Eccles, J. C., and Hoff, H. E.: The Rhythm of the Heart Beat. I. Location, Action Potential, and Electrical Excitability of the Pacemaker, *Proc. Roy. Soc. Lond.* 115 B: 307, 1934.
11. Hoff, H. E., and Nahum, L. H.: The Supernormal Period in the Mammalian Ventricle. *Am. J. Physiol.* 124: 591, 1938.

A NEW ELECTRODE FOR RECORDING BIOELECTRIC POTENTIALS

HOWARD L. ANDREWS, PH.D.*

LEXINGTON, KY.

THE electrodes described here were developed for use in the recording of electric potentials of cortical origin under conditions where ease of application and removal were of paramount importance. They were designed originally for use in a study of cortical potentials during the withdrawal phase of drug addiction, when the patient is highly irritable and objects to the use of collodion-cemented electrodes so commonly used in electroencephalography. These electrodes have proved so valuable for general use in electroencephalography and electrocardiography that a detailed description seems warranted.

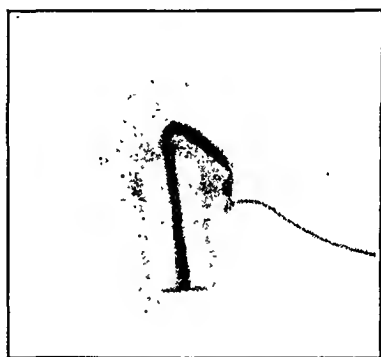


Fig. 1.—Roentgenogram of a completed electrode.

A disk 5 mm. in diameter with a thin tail 5 cm. long is cut from sheet silver about 0.5 mm. thick. The tail is bent up at right angles to the disk. The tail is then forced through the top of a rubber eraser of the type which slips over the end of an ordinary lead pencil. The tail is bent over and forced through the edge of the rubber at its thickest point. This prevents bending of the silver at the point where it emerges from the rubber. This point is sealed with wax to make a leak-proof joint. The lead wire is soldered to the silver near the point where the latter passes through the rubber rim. Fig. 1 shows a roentgenogram of a finished electrode. There are undoubtedly other rubber products available which would be suitable for making these suction cups. The erasers have been used because of their convenient size (contact area about 1 cm. in diameter), their availability, and low cost.

If these are applied to the scalp surface it is necessary to cut the hair over an area large enough to accommodate the end of the rubber cup. A

*Associate Physicist, United States Public Health Service, from the United States Public Health Service Hospital, Lexington, Ky.

Received for publication Oct. 27, 1938.

small amount of electrode jelly is placed in the cup and around the end. When squeezed to expel the air, pressed firmly against the skin and released, the cup will hold securely for at least an hour. When properly applied, these cups will withstand a surprising amount of pull and movement of the patient.

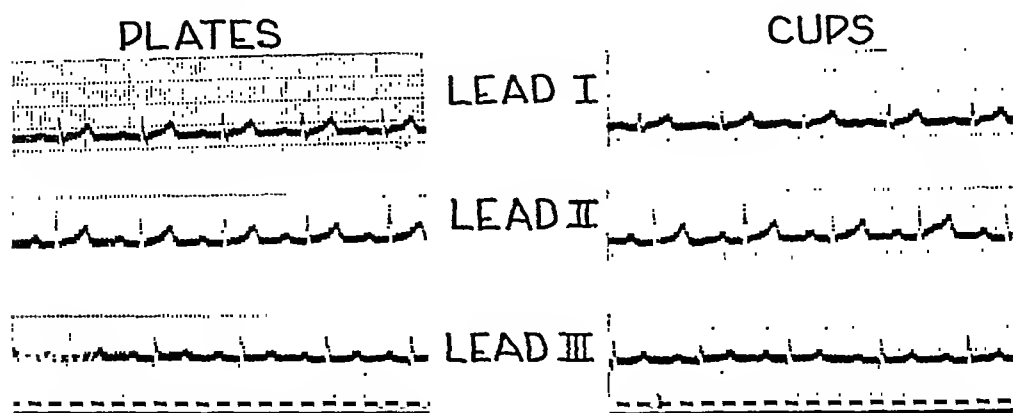


Fig. 2.—Comparison of plate and cup electrodes. In Lead I there is a low background of muscle potentials, but this is the only difference between the records.

If a nonpolarizable electrode is desired, a solution of 0.1 normal hydrochloric acid is quite satisfactory. Some of the solution is drawn up inside the cup and the latter arranged so that the end just dips into the solution. The cups are connected to the positive pole of a dry cell. A small piece of silver serves as the cathode. A satisfactory coat of silver chloride is obtained in three or four hours. If chlorided electrodes are used they should be kept moist when not in use to preserve the chloride coating. This is easily accomplished by using a short piece of rubber tubing just large enough to slip over the end of the rubber eraser. An excess of electrode jelly is placed in each suction cup and the latter is slipped into the tubing. If one cup is put in either end of the tubing air is excluded and the electrodes will be kept in good condition.

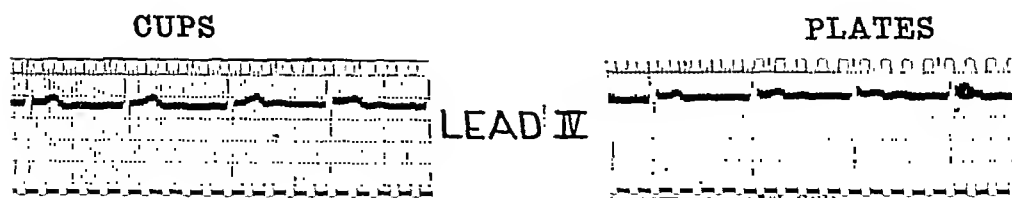


Fig. 3.—Comparison of Lead IV records taken with plates and cups. In the record taken with plates there is an overswing when the S-wave returns to the axis. This may be due either to electrode polarization or to the lack of precise localization of the apical point with the large electrodes.

Simultaneous electroencephalograms taken with a pair of collodion cemented electrodes and a pair of suction cups placed close to the cemented electrodes (but not in contact) showed no significant differences.

When used for electrocardiographic electrodes the disks can be made of zinc and no chloriding is necessary. In this application even a heavy growth of body hair does not interfere with the vacuum, so that no hair cutting is necessary.

Fig. 2 shows a series of consecutive electrocardiograms taken first with the regular plate electrodes and then with the suction cup electrodes. There are no important differences between the two sets of records.

In some cases there is a low amplitude background of muscle potentials in the suction cup records, but in no case is this objectionable, and in many cases it is absent. It can usually be removed by a slight change of the position of the cup.

The suction cup is particularly suited for the precordial contact in Lead IV. The desirability of keeping this electrode small has been emphasized in the report of the committee of the American Heart Association and the Cardiac Society of Great Britain and Ireland.^{1, 2}

When the region around the position of the apex beat is explored with one of the cup electrodes it is found that the records obtained show large variations from the records taken directly over the apex beat. Any large electrode will record an integrated effect which will differ from the true record obtained with the smaller electrode. Fig. 3 shows a comparison of Lead IV records taken with the small suction cup and with a plate 3 cm. in diameter. In this case the suction cup was nonpolarizable, and it is believed that the record from this electrode is a more accurate representation of the electrical activity existing at the apex.

If the electrocardiograms are recorded with a string galvanometer, with no intervening amplifier, the resistance of the small cups may cause trouble. The resistance between the pair of 1 cm. cups described is about 8,000 ohms. This is not high enough to cause trouble if they are connected to a vacuum tube amplifier. In cases in which electrode resistance was important, larger cups, 3 cm. in diameter, have been successfully used. A pair of these cups shows a resistance of about 1,500 ohms. Cups of the type used to fasten appliances to automobile windshields have a diameter of about 3 cm. and are quite satisfactory if low resistance contacts must be obtained.

I take this opportunity to express my appreciation to Dr. C. K. Himmelsbach for helpful suggestions and for critically reading the manuscript.

REFERENCES

1. Joint recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland, *J. A. M. A.* 110: 395, 1938.
2. Supplementary report of the Committee on Precordial Leads of the American Heart Association, *J. A. M. A.* 110: 681, 1938.

ENLARGEMENT OF THE HEART IN INFANTS AND YOUNG CHILDREN

M. A. KUGEL, M.D.

MIAMI BEACH, FLA.

CONGENITAL "idiopathic hypertrophy" of the heart is a term long used to designate cardiac enlargement with no apparent cause; upon pathologic investigation, only hypertrophy of the heart muscle is found. To anyone who has had experience at the autopsy table, the term "idiopathic hypertrophy," applied to great enlargement of the heart, seems very inappropriate. An organ does not enlarge beyond normal limits unless there is some underlying pathologic-physiologic disturbance, even though we may be unable to recognize it with our limited knowledge of today.

In a review of the literature¹ there was collected a series of cases of cardiac enlargement which were reported as instances of congenital idiopathic hypertrophy. A study of these cases, even as reported, revealed that most of them were not genuine examples of congenital idiopathic hypertrophy of the heart, since either myocardial disease or other factors were found in the post-mortem examination which could have had a causal relationship to the cardiac enlargement.^{2, 3}

In 1933, Kugel and Stoloff¹ described seven cases of unusual enlargement of the heart in infants and young children which hitherto might have been regarded as examples of idiopathic hypertrophy. In all instances the clinical picture and the pathologic changes in the myocardium were similar. Later, further investigation of fresh pathologic material with chemical examinations in another similar case confirmed the original impression that this form of cardiomegaly was different from von Gierke's disease and other types of cardiac enlargement (Table I).

TABLE I

CAUSES OF ENLARGEMENT OF THE HEART IN INFANTS AND YOUNG CHILDREN

I. *Congenital Defects*

- a. Heart
- b. Coronary arteries
- c. Aorta and pulmonary artery

II. *Infections*

- a. Unknown etiology { Rheumatic fever
Fiedler's myocarditis
Periarteritis nodosa, etc.
- b. Known etiology { Diphtheria
Scarlet fever, etc.
Subacute bacterial endocarditis, valvular defect
Syphilis, etc.

Dedicated to the late Dr. Louis Gross, brilliant investigator in the field of cardiovascular disease, teacher, collaborator, and friend.

Received for publication Nov. 1, 1938.

III. *Anemias (of long standing)*

- a. Primary anemia
- b. Secondary anemia

IV. *Syndrome of nonsuppurative "myocardial degeneration with dilatation and hypertrophy"*V. *Metabolic*

- a. Avitaminosis—beriberi, etc.
- b. Thyroid deficiency
- c. Glycogen-storage disease, von Gierke

VI. *Hypertension*

- a. Greater circulation

{	Essential Adrenal tumors Secondary to kidney lesions (inflammatory or congenital)
---	--
- b. Lesser circulation (lesions in lung, kyphoscoliosis, etc.)

VII. *Tumors of Heart*

- a. Primary
- b. Secondary

VIII. *Unclassified Group*

CASE REPORT

G. H., Case No. 8, an 8-month-old colored girl who had previously been well, was admitted Nov. 22, 1934, to the Mount Sinai Hospital on the service of Dr. Bela Schick with a history of a cough for one week previous to admission. The cough had become worse in the preceding two days, and had occurred in paroxysms, often lasting an hour or more. At no time did the child appear acutely ill. When she was examined by the family doctor there was only a slight fever and the throat was slightly red. The doctor stated that the "chest was clear." Argyrol was applied locally to the nose.

The mother, 25 years of age, was living and well; she had had one miscarriage, which occurred at the third month of gestation. There were no other children. There was no apparent history of tuberculosis, syphilis, or other diseases. Both parents were colored.

The child was born in New York City, at full term. The delivery was normal. The baby weighed 7 pounds and showed no evidence of cyanosis or icterus. It breathed and nursed normally and was breast-fed until it was 5 months old. The diet was then supplemented by cow's milk. Orange juice had been given since the child was 3 months old, and cod-liver oil (a teaspoonful three times a day) for the preceding four to five months. It gained normally. The child had had occasional colds.

On examination the child appeared to be acutely ill. She had an almost continuous high-pitched cough. There were dyspnea and cyanosis. The temperature was 97.6° F.; the respiration rate 44. There were many vesicular lesions, some of which were pustular, over the anterior part of the thorax, the neck, and forehead. There were enlarged lymph nodes at both angles of the jaw, and in the posterior cervical, inguinal, and epitrochlear regions. There was an area of dullness extending over the left anterior chest to the axilla. Many crepitant and subcrepitant râles were heard, most marked on the left side. The heart rate was 160 and the rhythm was normal. The heart sounds were poor in quality. The blood pressure was 72 systolic. The abdomen was protuberant. The spleen was soft, extending one fingerbreadth below the costal margin. The liver was two fingerbreadths below the costal margin.

Roentgenologic examination of the chest showed a very marked enlargement of the heart to the left, extending out to the axilla; on the right side it extended to the midclavicular line. The enlargement also involved the entire base (Fig. 1).

A certain amount of magnification and distortion of the heart shadow was due to the fact that the examination could be made only in the anteroposterior position; the usual standard method could not be used.

An electrocardiogram taken Nov. 23, 1934, showed sinus tachycardia with a rate of about 150 beats per minute, low amplitude of QRS in Lead I, and T waves of low amplitude (Fig. 2).

On Nov. 23, 1934, the child was seen in consultation by the author and a diagnosis of primary myocardial degeneration with dilatation and hypertrophy of the heart was ventured because of lack of the usual signs of congenital cardiac defects, as well as of evidence of diseases such as rheumatic fever, diphtheria or beriberi.



Fig. 1.—Case 8. Roentgenogram of chest showing marked enlargement of heart with dilatation of left ventricle and some prominence of right border.

The sugar content of the blood was 65 mg. per cent, the urea 11 mg. per cent, the cholesterol 235 mg. per cent, and the cholesterol ester 75 mg. per cent. The blood Wassermann reaction was positive (4 plus) on two occasions. The blood Kahn test was negative. The urine was normal. The hemoglobin was 60 per cent, the erythrocyte count 3,640,000, and the leucocyte count 32,000; the differential leucocyte count showed 46 per cent polymorphonuclear leucocytes, of which 2 per cent were myelocytes and 1 per cent eosinophiles. Examination of the blood smear revealed some hypochromia and toxic granules in a few of the polymorphonuclear leucocytes.

The child showed no signs of improvement throughout her stay in the hospital and died of myocardial failure on Nov. 25, 1934.

The clinical diagnosis was (1) enlargement of the heart (so-called "congenital hypertrophy"), (2) rickets, and (3) miliaria.

Post-mortem examination was performed under the direction of Dr. Paul Klemperer. The findings were as follows: The body of the poorly developed and undernourished 8-month-old female colored child showed no evidence of jaundice or edema. The abdomen was distended, with a slight bulge at the umbilicus. The liver's edge reached down to the level of the umbilicus and the liver occupied the

entire upper abdomen, displacing the spleen posteriorly. The spleen was also enlarged, extending to the level of the umbilicus. The heart was markedly enlarged. The left ventricle extended almost to the left lateral thoracic wall, displacing and compressing the left lung laterally and posteriorly. The right border, formed by the bulging right auricle and enlarged right ventricle, was in the region of the right midclavicular line.

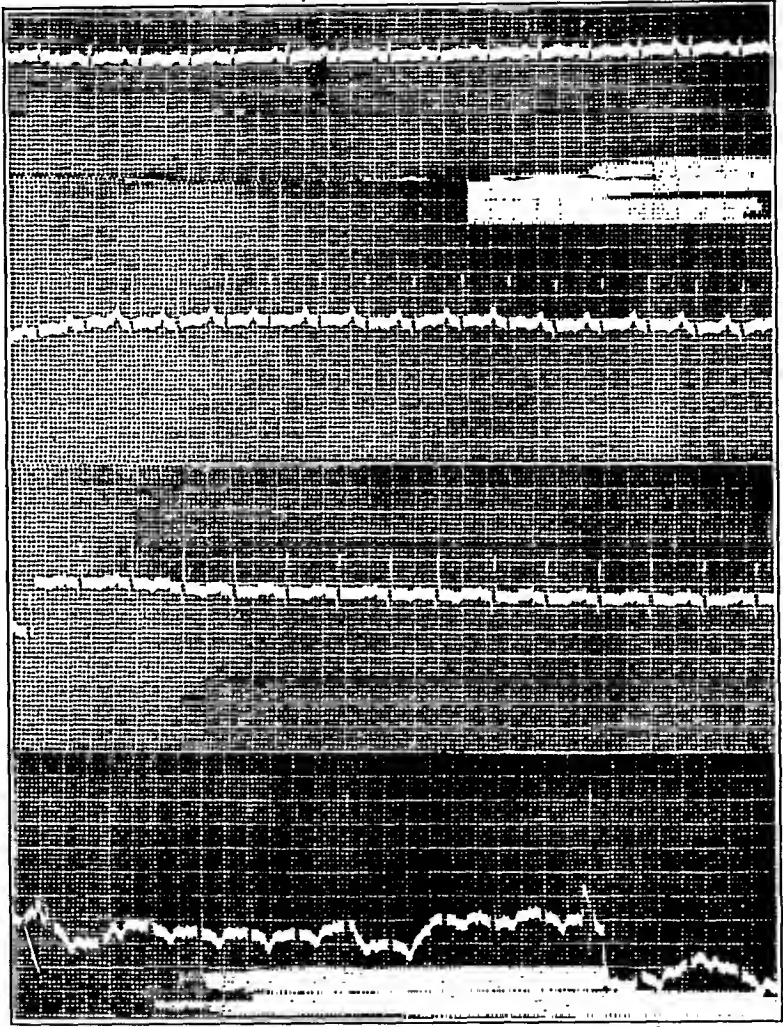


Fig. 2.—Case 8. Electrocardiogram showing sinus tachycardia, QRS of low amplitude, in Lead I, and T waves of low amplitude, indicating myocardial involvement.

The heart weighed 90 gm. (Fig. 3). On the anterior aspect of the pericardial sac there was a diffuse hemorrhagic area (ante-mortem pericardial puncture). The pericardial sac contained a small amount of clear straw-colored fluid and was otherwise entirely occupied by the enlarged heart. The coronary veins were congested and prominent beneath the visceral pericardium. The epicardial surface of the upper posterior portion of the left ventricle was discolored, presenting a dark, reddish, mottled aspect over an area 3 by 4 cm. in size. The right auricle was markedly dilated and its wall slightly hypertrophied. The right ventricle was also markedly dilated and somewhat hypertrophied. The trabeculae carneae were prominent. The myocardium of the right ventricle measured 4 mm. in thickness at its midportion, and 3 mm. at the apex. The left ventricle was markedly dilated. Its walls were hypertrophied. The myocardium of the left ventricle measured 7 mm. in thickness

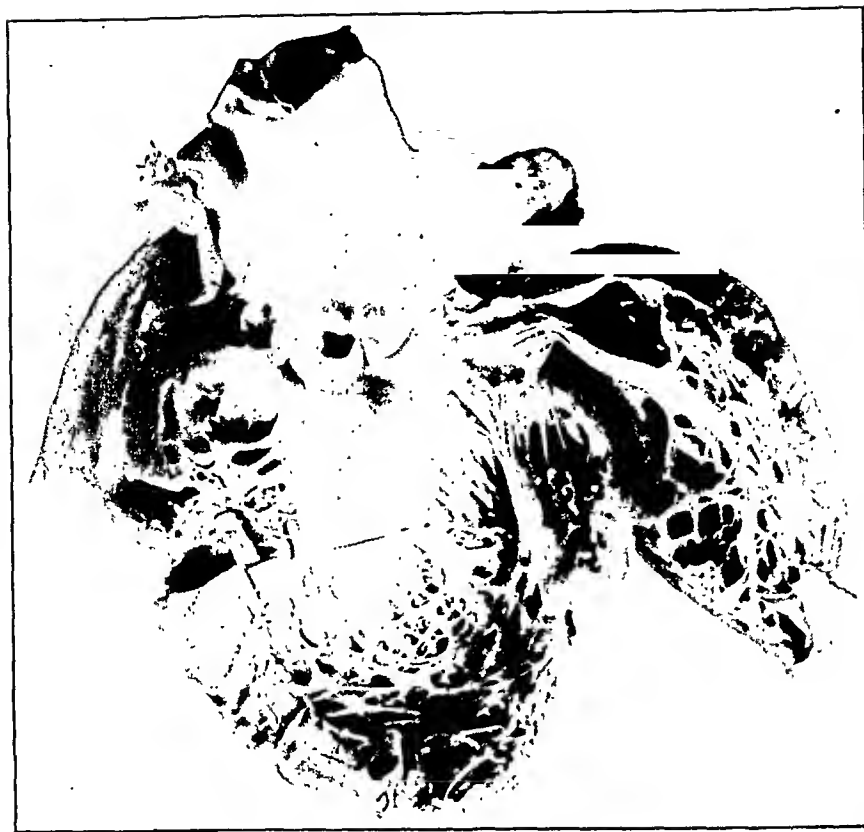
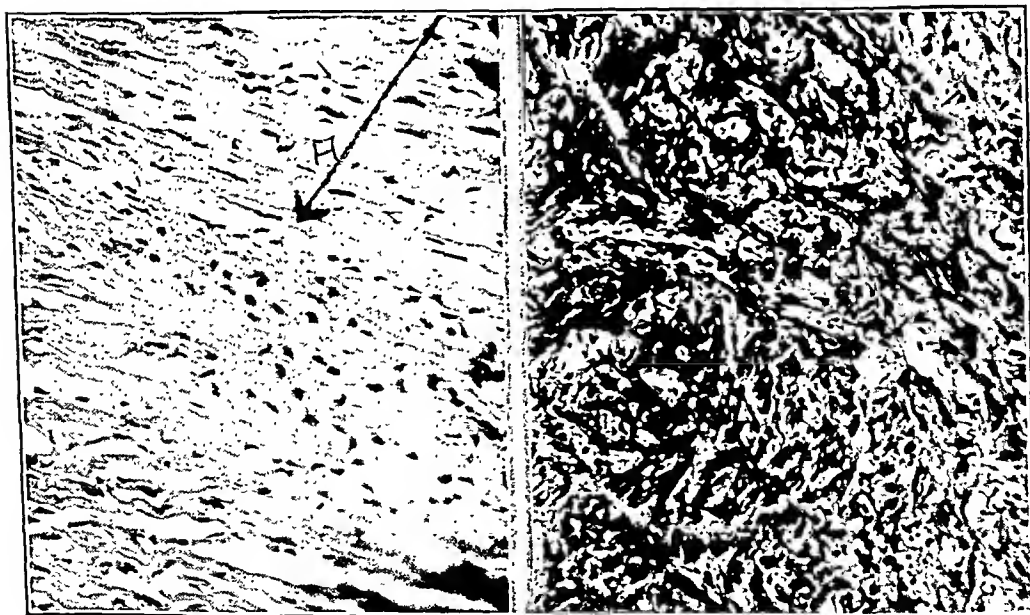


Fig. 3.—Case 8. Photograph of enlarged heart showing dilatation and hypertrophy of the left ventricle and appearance of myocardium.



A.

B.

Fig. 4.—Case 8. Photomicrographs of ventricular musculature of heart showing (A, see arrow) focus of myocardial degeneration and (B) distortion of muscle fibers.

at its midsection and 5 mm. at the apex. The outflow tract of the left ventricle measured 4.8 cm. in diameter. The myocardium, on section, was dull, pale, and grayish-brown throughout. The endocardium of the left ventricle was thickened and whitened. The valves presented no gross changes. The foramen ovale was small. The coronary ostia were patent and normal in origin and distribution. The ductus arteriosus was obliterated. The aorta showed no abnormalities. The lungs were the seat of a bronchopneumonia.

The liver, light yellow-brown in color, was large, and its surface was smooth and glistening. The spleen was large and firm. The kidneys were slightly enlarged. The thymus was not enlarged. The bone marrow was cellular, red in color, and had normal bone trabeculae. The costochondral junction presented a distinct narrow line. The osteochondral boundary at the head of the humerus (left) was also fine and distinct. The periosteum of the upper humerus (left) showed no gross changes.

Microscopic Examination.—The lung sections showed bronchopneumonia. The myocardium showed focal areas of degeneration (Fig. 4). In the vicinity of the fibrous areas in the myocardium there were occasional muscle fibers with vacuoles. Some of the muscle fibers showed atrophy and degeneration with replacement fibrosis. There were no areas of suppurative cellular infiltration. The blood vessels showed no marked changes. A few lymphocytes were found in the pericardium. The endocardium was thickened.

The liver contained a small amount of fat. The kidneys were negative, as also were the adrenals, pancreas, spleen, and lymph nodes. The skeletal muscle was negative.

Glycogen stains showed only a moderate amount of glycogen, uniformly and normally distributed, in the heart, lungs, liver, kidneys, and skeletal muscle. There was no clinical, pathologic, or chemical evidence of von Gierke's disease. Sudan stains revealed only a small amount of fat. The Levaditi stains for spirochetes in the heart and kidneys were negative, and a thorough gross and microscopic examination failed to reveal evidence of congenital syphilis.

Post-Mortem Diagnosis.—Cardiac dilatation, (marked), all chambers; cardiac hypertrophy (moderate); acute congestion of liver, spleen, kidneys; fatty changes in liver; partial atelectasis of lungs, including all lobes; bronchopneumonia.

This case, No. 8, just described in detail, proved to be very important. The clinical picture and pathologic lesions were similar to those in our seven cases previously reported.¹ In the eighth case, however, we were able to make chemical, as well as microscopic, studies of fresh heart muscle, skeletal muscle, and other organs, and definitely ruled out abnormal glycogen-storage disease. A study of this group of eight cases has enabled us to recognize this form of cardiomegaly clinically.

SUMMARY OF THE CLINICAL AND PATHOLOGIC FINDINGS IN THE SYNDROME OF NONSUPPURATIVE MYOCARDIAL DEGENERATION WITH DILATATION AND HYPERTROPHY

Definition.—A well-defined syndrome in infants and young children characterized clinically by an unusual degree of enlargement of the heart, electrocardiographic abnormalities, an afebrile course, a tendency to abrupt onset of myocardial failure, and the suddenness with which death may occur.

Etiology.—The etiology of this disease is at present undetermined. Many theories have been advanced but none proved.¹ In most of the cases the disease has been recognized before the second year of life (Table II).

TABLE II
SUMMARY OF EIGHT CASES OF CARDIAC ENLARGEMENT ASSOCIATED WITH
NONSUPPURATIVE MYOCARDIAL DEGENERATION

CASES	1	2	3	4	5	6	7	8
Age	8 mo.	6 mo.	3 mo.	15 mo.	4 mo.	3 mo.	6½ yr.	8 mo.
Sex	M	M	F	M	M	M	F	F
<i>Symptoms</i>								
Dyspnea		x	xxx		x	xxx	xxx	
Cyanosis		x	xxx	x	x		x	x
Vomiting	xxx	xxx		xxx			xx	
Cough				x				xxx
Total known duration of illness	6 wk.	1 day	4 days	2 wk.	5 days	1 day	10 wk.	6 days
<i>Heart Weight in Grams</i>								
Normal (average)	33	32	22	45	22	22	84	33
*Actual	75	90	Marked enlargement	155	85	75	190	90

*Percentage increase of actual heart weight compared to normal standards was from 120 to 290 per cent.

The disease is apparently not limited to any sex or race. We have observed two cases in adults in which the lesions were similar. Some of those reported by Levy⁴ may belong to this group.

The changes in the heart may represent an allergic response to infection, probably due to a virus. Whether this is a specific reaction to a specific infection, or an allergic response to various types of infections, is at present undetermined. The possible factor of infection is the only consistent one we have had.¹ It has also been suggested that these lesions may represent an allergic reaction to milk in a heart which was already damaged by infection.⁵

Symptoms.—The early symptoms of this disease are as yet not too well defined. The respiration may be rapid without any apparent intrathoracic cause. The dyspnea and cyanosis, however, are usually of sudden onset. Fever is generally absent, and the temperature remains normal unless there are complicating independent infections. The heart rate is usually rapid, and the heart sounds are of poor quality. At times a soft, blowing, systolic murmur may be heard at the apex. The cardiac enlargement may not be discovered by physical examination, but roentgenograms of the chest will reveal, usually, a surprising degree of enlargement of the heart.

In the terminal stages of this disease the liver is enlarged. Râles may be heard in the chest, and at times edema occurs. The most striking fact about this entire clinical picture is that the infants or children are usually apparently well and then suddenly develop myocardial

failure, ery, vomit, or refuse food. Unless the chest is examined carefully, the true nature of this condition may not be appreciated.

Roentgenologic examination shows enlargement of the heart to the left and somewhat to the right (Fig. 1). It may be so marked as to fill almost completely the left side of the chest in its transverse diameter. The value of the roentgenologic examination in cases of unexplained dyspnea and cyanosis becomes apparent, since it may reveal a pronounced enlargement of the heart, frequently in the absence of suggestive physical signs. Although the roentgenographic appearance is strikingly suggestive, it is by no means pathognomonic. A similar shadow may be cast in dilatation and hypertrophy of the heart in cases of valvular disease, congenital anomalies, or marked anemia. However, the enlargement of the left auricle and the rumbling murmurs of mitral stenosis, found in rheumatic cardiovalvular disease, are lacking.

Two patients were examined by means of the electrocardiograph and both showed evidence of myocardial damage, such as low voltage, shallow T waves, or prolongation of the P-R interval.

Course and Prognosis.—In five of our cases the patient died on the day of admission. The total duration of illness was usually short (Table II). In two cases it was one day, in one case four days, in another five days, in another six days, in one case two weeks, in another six weeks, and in another ten weeks. Apparently the duration of the disease bears some relationship to the age of the patient. It seems that the older the patient, the longer the disease lasts.

Morbid Anatomy.—The lesions were similar in all of the eight cases. The hearts were dilated and hypertrophied and the weight greatly increased. The endocardium of the left auricle and left ventricle may be thickened. At times bland thrombi may be found attached to the ventricular endocardium in the interstices between the trabeculae carneae. There are no valvular or congenital defects.

On cutting the myocardium, one can see grossly, in some instances, grayish streaks which on microscopic examination prove to be foci of atrophied and degenerated muscle fibers. Atrophy of the muscle fibers with fatty infiltration, muscle degeneration, and replacement fibrosis are the characteristic lesions in all cases. Occasionally a few lymphocytes are found. There are no suppurative foci. The heart muscle arrangement may be so distorted and scarred that it is difficult to recognize (Fig. 4B). The coronary arteries showed variable changes, from perivascular fibrosis to hypertrophy of the media and proliferation and desquamation of the intima which at times is sufficient to obliterate the lumen. The valves were in all instances normal. In one instance we found embolic glomerular lesions which could be traced to bland thrombi on the ventricular endocardium.

In our eighth case we found small isolated foci of degenerated heart muscle surrounded by apparently normal myocardium (Fig. 4A). This represents probably the earliest lesion of this disease. Even in these

foci there were only a few pyknotic nuclei and wandering cells. Glycogen stains of the myocardium, lungs, liver, and kidneys showed either a small amount, which is normal, or none at all. Sudan stains showed very little fat, while the Levaditi stains showed nothing.

Treatment.—At present little can be said concerning treatment. All of our eight patients died, six within less than a week after admission. Our observations in Case 7 and in two cases in adults, in which symptoms of myocardial failure lasted from ten weeks to three years, give some hope for prognosis and therapy. Prolonged rest, instituted early, and the administration of proper doses of digitalis may have helped in some of these cases. Our only hope in therapy is in the early recognition and the appreciation of the clinical significance of the various types of cardiac enlargement in children.

Diagnosis.—A presumptive diagnosis of the syndrome of cardiac enlargement associated with nonsuppurative myocardial degeneration and fibrosis can be made during life. After clinical and pathologic studies of our first few cases, we were able to predict the presence of this peculiar malady in five instances, in all of which the diagnosis was confirmed at autopsy.

The chief features of this condition are enlargement of the heart without known cause, an afebrile course, the sudden onset of symptoms, dyspnea and cyanosis, and the lack of signs or history suggestive of congenital heart disease, rheumatic fever, diphtheria, infections, anemia, or metabolic disturbances.

DIFFERENTIAL DIAGNOSIS

Congenital Heart Disease.—The finding of an enlarged heart in an infant or a child brings up the problem of differential diagnosis (Table I). Cardiac enlargement in the first few years of life is not infrequently due to a congenital malformation of the heart.⁶⁻⁹ Congenital heart disease, as outlined in the classical monograph of Abbott,⁶ is divided into three clinical groups: (1) the *acyanotic* group, with no abnormal communications between the various chambers of the heart, (2) the *cyanose tardive* group, with an arteriovenous shunt in the circulation and a terminal reversal of blood flow, and (3) the *cyanotic* group, with a permanent venous-arterial shunt and a retardation of blood flow.

Symptoms usually present themselves early in children with congenital heart disease who belong to the cyanotic group. The murmurs heard in this type of congenital cardiac disease are usually loud and rumbling. Roentgenologic examination of the heart may reveal that its outline is bizarre. The contour of the right ventricle, right auricle, pulmonary artery, or aortic conus may be distorted. The electrocardiogram may show right ventricular predominance or other evidences confirming the diagnosis of congenital heart disease.

In the syndrome of cardiac enlargement described, the symptoms usually occur in a child who apparently has been well. Cyanosis in

this instance is only terminal and then not marked. The heart sounds are muffled and at times one hears a soft, blowing murmur at the apex. Roentgenologic examination shows enlargement chiefly of the left ventricle. The left auricle, pulmonary conus, and aortic conus are normal.

It is in the acyanotic group where one finds cases of cardiac enlargement in which the clinical picture is similar to that described by the author. Congenital anomalies of the coronary arteries, such as malposition or maldevelopment, which cause myocardial degeneration, may be followed by marked enlargement of the heart. Such cases have been reported, but are extremely rare.^{8, 9}

Abrikosoff⁸ was the first to describe a case of this nature. In his case the origin of the right coronary artery was normal, but the left coronary artery originated from the pulmonary artery instead of the aorta. At autopsy there was a marked enlargement of the heart, with an aneurysmal dilatation of the left ventricle. The wall of the left ventricle near the apex was very thin and transparent and was replaced by fibrous tissue.

Bland, White, and Garland⁸ have encountered only eight cases in which one of the main coronary arteries, usually the left, arose from the pulmonary artery. In addition, they also report a case of unusual enlargement of the heart associated with congenital anomalies of the coronary arteries.

The clinical diagnosis was "congenital idiopathic hypertrophy" of the heart. Necropsy studies, however, revealed the true nature of the disease. The heart weighed 91 gm. The left ventricle was enlarged and its endocardium showed marked fibrous thickening with occasional patches of fibrosis in the deeper layers. In this case the left coronary artery had its abnormal origin from the pulmonary artery. Had a complete investigation, including post-mortem examination, not been made, this case might have been reported as one of "congenital idiopathic hypertrophy," and this unfortunate term perpetuated in the literature.

In this group we are dealing with a nonsuppurative myocardial degeneration with replacement fibrosis, and the cause of the myocardial damage can be traced to abnormalities in the coronary arteries. In the syndrome described, the cause of the myocardial degeneration is still undetermined. In both instances, however, we have the same pathologic physiology, and therefore it is not surprising that we have the same clinical picture.

Rheumatic Fever.—Enlargement of the heart because of rheumatic infection may be found early in childhood. Rheumatic heart disease occurs in infants and young children more frequently than is generally appreciated. Taran,¹⁰ in a study of 222 children between the ages of 1 and 15 years, found that the highest incidence of rheumatic infection in childhood occurs during school age, that is, from 6 to 15 years. He also found forty cases in infants less than 1 year of age reported in the

literature. Coronary thrombosis of rheumatic origin has been reported in an infant 17 months old.¹¹

Poynton¹² found cases of rheumatic heart disease early in life. In a review of 100 patients with acute rheumatism admitted to his ward at the Hospital for Sick Children, he found that thirteen had had the first attack between the ages of 2 and 5 years. Poynton also reports observations on a child of 10 months who had chorea and "acute dilatation" of the heart.

The diagnosis of rheumatic fever in infants and young children can be made if one keeps in mind the fact that this disease can strike early in infancy in the most bizarre fashion. A familial history of rheumatic fever should arouse the suspicion of the presence of this disease in a child with cardiac enlargement.¹³⁻¹⁵ The other signs and symptoms to be looked for are: fleeting pains in the joints or muscles; spasmodic twitchings (choreiform movements); and abdominal manifestations, such as cramps or, at times, symptoms simulating intra-abdominal inflammation. Evidence of tonsillitis, pharyngitis, polyarthritides, pancreatitis, and myocarditis may be found. Also, there may be continued fever, leucocytosis, abnormal sedimentation time, electrocardiographic changes, etc., which help to establish the diagnosis. When there is a marked enlargement of the heart there is usually a history of rheumatic manifestations. The murmurs are loud and rumbling. Roentgenologic examination may show typical mitralization of the heart, with an enlarged left auricle. The lesions in the myocardium in a case of rheumatic fever are so well known that they need not be described here.

Fiedler's Myocarditis.—Scott and Saphir,¹⁶ in 1929, reviewed thirty cases from the literature. Only two were in children 10 years of age, or younger. One child was 3 years old, and the other was 6. In both cases the heart was enlarged. This disease is extremely rare in infants and young children. Excellent monographs with complete bibliography are available.¹⁶⁻¹⁸ These individuals may have a low-grade fever, signs of myocardial failure, and definite electrocardiographic changes. The heart is the seat of an acute isolated myocarditis and the lesions are characteristic.

Infections of Known Etiology.—The heart may be enlarged when affected by diphtheria, scarlet fever, bacterial endocarditis, syphilis,¹⁹ and other bacterial infections.^{20, 21} The problem of differential diagnosis here is a question of the recognition, or the ruling out, of infections of known bacterial origin. The question of other rare forms of myocarditis²¹ comes up only when the history indicates such a possibility.

Anemia.—Enlargement of the heart in infants and young children can occur in severe anemia.²² While in Puerto Rico, visiting Bailey K. Ashford, the author was shown children suffering from hookworm infestation, complicated by severe anemia. The hearts of these malnourished children were apt to be enlarged, and apical systolic murmurs were heard. It was Dr. Ashford's observation that the heart returned to

normal size and the murmurs disappeared when the hemoglobin returned to normal (after the hookworm disease was alleviated or the malnutrition corrected). Similar observations have been reported in adults.²⁵

Beriberi.—Vitamin deficiency may lead to beriberi with enlargement of the heart. This may occur in cases of malnutrition and should be suspected particularly in those children who are deprived of proper foods and have enlargement of the heart with symptoms of myocardial failure. The differential diagnosis can be made by a therapeutic test. These patients do not respond to the ordinary treatment for myocardial failure, such as xanthine diuretics or digitalis, but do recover when vitamin B is administered.

Von Gierke's Disease.—This is a disorder of infants or young children, due to a disturbance of dextrose metabolism.^{24, 25} The most striking feature of this disease is the enlargement of the liver, kidneys, or heart. The cause of the enlargement is the accumulation of glycogen, in abnormal amounts, in the parenchymal cells. The clinical manifestations depend upon the extent of the damage to the involved organs. Clinically, there are two types: (1) hepatic, and (2) cardiac. The number of reported cases of the cardiomegalic type of von Gierke's disease is still very few. Kato²⁵ found that in no case of cardiomegaly of the von Gierke type had the diagnosis been made during life. Usually this disease occurs in infants 1 year of age, or younger.

Clinically, there may be a markedly enlarged heart with progressive myocardial failure. Colds or infections often precede the onset of myocardial failure, which is manifested by rapid breathing, cyanosis, and edema. In the case reported by Antopol,²⁴ breathing had been unusually rapid ever since birth. There may be generalized weakness. The electrocardiographic findings in the case of Dr. White³ were normal. A normal electrocardiogram, in addition to chemical studies, may be the means of differentiating von Gierke's disease from other types of cardiomegaly.

The diagnosis in the hepatic type has been made by biopsy of the liver. Also, in these cases one may encounter acetoneuria, ketonuria, etc. "One of the most unusual features has been the failure of the adrenalin to induce an appreciable increase in blood sugar or blood lactic acid or to diminish ketonuria."²⁵ The blood sugar in the fasting states has been found to be low. Chemical studies should be made in all cases of cardiomegaly in children when the etiology is obscure, in order to rule out von Gierke's disease.

Post-mortem studies have helped to clarify this condition. At autopsy, it is not difficult to differentiate glycogen-storage disease from other forms of cardiomegaly. In the cardiomegalic group the size of the heart may be more than four times the normal. The enlargement is caused by marked hypertrophy. The walls of the ventricles are thickened and the ventricular cavities appear small. The myocardium is firm and thick, and on cross section appears "reddish-pink, mottled with pinkish grey."²⁵ The liver and kidneys may be enlarged.

On microscopic examination of the heart one finds a diffuse vacuolization of the muscle fibers. On cross section "the muscle cells appear in the form of hollow cylinders surrounded by delicately striated protoplasmic walls."²⁴ According to Kato,²⁵ "many, if not all, of the children of the cardiac group had a similarly moderate involvement of the liver and kidneys." The skeletal muscle may also be the seat of such lesions. Glycogen stains made on fresh material, properly fixed, reveal glycogen storage in the heart, liver, kidneys, or skeletal muscle in abnormal amounts. Kato²⁵ warns, however, that we must avoid the error of attaching too much significance to the presence of small amounts of glycogen, even in enlarged organs.

Hypertension.—Enlargement of the heart associated with hypertension, either primary or secondary, has been found in children. Hypertension following rheumatic fever^{26, 27} or associated with suprarenal tumors²⁸ presents a definite clinical picture for differential diagnosis. In cases of spinal deformities, hypertrophy and dilatation of the heart may occur.^{29, 30} In these instances the enlargement of the heart is usually right-sided, and is believed to be secondary to hypertension of the lesser circulation.

SUMMARY

The cause of enlargement of the heart in infants and young children is still a fertile field for investigation. Only in recent years has it been demonstrated that in many cases what was formerly called "idiopathic hypertrophy" of the heart was in reality associated with congenital malformations, rheumatic fever, glycogen-storage disease, myocardial degeneration and fibrosis, etc.

Eight cases of enlargement of the heart in infants and young children, presenting a definite clinical syndrome, have been described (one herein and seven in a previous paper¹).

Cases of dilatation and hypertrophy of the heart, associated with myocardial degeneration and fibrosis, are by no means rare. They constitute the greatest number of those formerly included under the title of "idiopathic hypertrophy."^{1, 5}

The differential diagnosis of the various forms of cardiomegaly has been briefly outlined.

A tentative classification of the various forms of enlargement of the heart has been suggested.

It has been emphasized that the term "congenital idiopathic hypertrophy" of the heart is not only undesirable but also confusing. In most instances the cause or nature of the enlargement of the heart in an infant or young child can be determined if the various criteria or diseases, as outlined, are kept in mind.

The author is indebted to Dr. Bela Schick for the use of the clinical material from his service at the Mount Sinai Hospital of New York City.

REFERENCES

1. Kugel, M. A., and Stoloff, E. G.: Dilatation and Hypertrophy of the Heart in Infants and Young Children, *Am. J. Dis. Child.* 45: 828, 1933.
2. Howland, John: Idiopathic Hypertrophy of the Heart in Young Children, *Contributions to Medical and Biologic Research*. Dedicated to Sir William Osler, July 12, 1919.
3. Sprague, Howard B., Bland, Edward F., and White, Paul D.: Congenital Idiopathic Hypertrophy of the Heart, *Am. J. Dis. Child.* 41: 877, 1931.
4. Levy, Robert L., and von Glahn, William C.: Further Observations on Cardiac Hypertrophy of Unknown Etiology in Adults, *Tr. A. Am. Physicians* 52: 259, 1937.
5. Mahon, George S.: Idiopathic Hypertrophy of the Heart With Endocardial Fibrosis, *AM. HEART J.* 12: 608, 1936.
6. Abbott, Maude E.: *Atlas of Congenital Cardiac Disease*, Am. Heart A., New York, 1936.
7. Kugel, M. A.: Congenital Heart Disease, *AM. HEART J.* 7: 262, 1931.
8. Bland, Edward F., White, Paul D., and Garland, Joseph: Congenital Anomalies of the Coronary Arteries: Report of an Unusual Case Associated With Cardiac Hypertrophy, *AM. HEART J.* 8: 787, 1933.
9. Levine, Harold D.: Cardiac Hypertrophy in Infancy, *Am. J. Dis. Child.* 48: 1072, 1934.
10. Taran, Leo M.: Rheumatic Cardiac Disease in Childhood, *Am. J. Dis. Child.* 50: 840, 1935.
11. Gross, Louis, Kugel, M. A., and Epstein, E. Z.: Lesions of the Coronary Arteries and Their Branches in Rheumatic Fever, *Am. J. Path.* 11: 253, 1935.
12. Poynton, John F.: *Lettsomian Lectures on Rheumatic Heart Disease in Childhood*, Tr. Med. Soc. London, Vol. LI, 1928.
13. Fischer, Vincent E.: Rheumatic Heart Disease at One Year, *Am. J. Dis. Child.* 48: 590, 1934.
14. Paul, John R.: Age Susceptibility to Familial Infection in Rheumatic Fever, *J. Clin. Investigation* 10: 53, 1931.
15. Paul, John R., and Salinger, Robert: The Spread of Rheumatic Fever Through Families, *J. Clin. Investigation* 10: 33, 1931.
16. Scott, R. W., and Saphir, Otto: Acute Isolated Myocarditis, *AM. HEART J.* 5: 129, 1929.
17. De la Chapelle, Clarence E., and Graef, Irving: Acute Isolated Myocarditis, *Arch. Int. Med.* 47: 942, 1931.
18. Simon, Morris A., and Wolpaw, Sidney: Acute, Subacute and Chronic Isolated Myocarditis, *Arch. Int. Med.* 56: 1136, 1935.
19. Saphir, O.: Syphilitic Myocarditis, *Arch. Path.* 13: 266, 436, 1932.
20. Swift, Homer F.: The Heart in Infection, *AM. HEART J.* 3: 629, 1928.
21. Rothschild, Marcus A.: Myocarditis, *Contribution to Libman Anniversary Volume*, October, 1932.
22. Nemet, Geza, and Gross, Harry: Cardiac Hypertrophy in a Case of Cooley's Anemia, *AM. HEART J.* 12: 352, 1936.
23. Ball, David: Changes in the Size of the Heart in Severe Anemia, *AM. HEART J.* 6: 517, 1931.
24. Antopol, William, Heilbrunn, Julius, and Tuchman, Lester: Enlargement of the Heart Due to Abnormal Glycogen Storage in Von Gierke's Disease, *Am. J. M. Sc.* 188: 354, 1934.
25. Humphreys, Eleanor M., and Kato, K.: Glycogen-Storage Disease, *Am. J. Path.* 10: 58, 1934.
26. Taussig, Helen B., and Hecht, Manes S.: Studies Concerning Hypertension in Childhood, *Bull. Johns Hopkins Hosp.* 62: 482, 1938.
27. Taussig, Helen B., and Hecht, Manes S.: Studies Concerning Hypertension in Childhood, *Bull. Johns Hopkins Hosp.* 62: 491, 1938.
28. Oppenheimer, B. S., and Fishberg, Arthur M.: The Association of Hypertension with Suprarenal Tumors, *Arch. Int. Med.* 34: 631, 1924.
29. Edeiken, Joseph: The Effect of Spinal Deformities on the Heart, *Am. J. M. Sc.* 186: 99, 1933.
30. Reid, William D.: Spinal Deformity as Cause of Cardiac Hypertrophy, *J. A. M. A.* 94: 483, 1932.

BODY BUILD AND HEART SIZE

A STUDY OF TWENTY PAIRS OF IDENTICAL TWINS AND FIFTEEN PAIRS OF UNRELATED INDIVIDUALS WITH SIMILAR BODY HEIGHT AND WEIGHT

WILFRID J. COMEAU, M.D., AND PAUL D. WHITE, M.D.

BOSTON, MASS.

THERE have been a number of clinical and anatomic studies in which various body measurements have been correlated with the size of the normal heart. Roesler,¹ in his recent text on cardiovascular roentgenology, gives an excellent, comprehensive, and critical summary of this material. It is generally agreed that, of the body measurements, body weight and body surface area give the highest degree of correlation with heart size. Body height, as a criterion, has been found to be of much less significance, while age, in the adult, has no value as a correlation factor. In view of the interest in the correlation of isolated somatic measurements with the size of the heart, it is surprising that more data are not available on heart size in individuals of similar body build.

The ideal group for such a study is, of course, identical twins. Although twins have been a source of anthropometric interest in other respects, there exists little information about the cardiovascular system other than a few general statements that the shape of the heart, the pulse rate, and the blood pressure are not infrequently quite similar in identical twins. We have found no published data which deal specifically with heart measurements in twins other than two reports in the German literature, one by von Vershuer and Zipperlen² and the other by Gurewitsch,³ although Weitz,⁴ without presenting measurements, does make a general statement, based on orthodiagrams, that the hearts of identical twins resemble each other very closely. Curtius (quoted by Gurewitsch) bases a similar conclusion on the size of the heart as determined by percussion. The studies of von Vershuer and Zipperlen and of Gurewitsch are not without objection, since they both made only one measurement, the transverse diameter of the heart. Furthermore, their principal interest was an evaluation of such factors as heredity, environment, and childhood diseases, on variations in the shape and size of the heart rather than an evaluation of the influence of body structure.

It seems justifiable to assume that the body build of a pair of identical twins will be much more similar than will be the case in two unrelated individuals of the same height and weight. However, in view

From the Cardiac Clinic and Laboratory of the Massachusetts General Hospital, Boston.

Received for publication Nov. 11, 1938.

of the fact that the objection might be raised that apart from body structure genetic influences per se might have a direct influence on the size of the heart, it seemed highly desirable to compare the data on twins with the data concerning a group of pairs of unrelated individuals of the same sex with similar body height and weight.

MATERIAL AND METHOD

In each instance the twenty pairs of twins were regarded as identical because of the very close similarity of their general appearance and of other gross physical characteristics. The fifteen pairs of unrelated individuals were chosen from a large group of subjects on whom determinations of heart size had been made for another purpose. These unrelated pairs were selected only on the basis of identical sex and of close similarity in body height and weight. In both groups the hearts were clinically normal and the individuals were in a good state of general health.

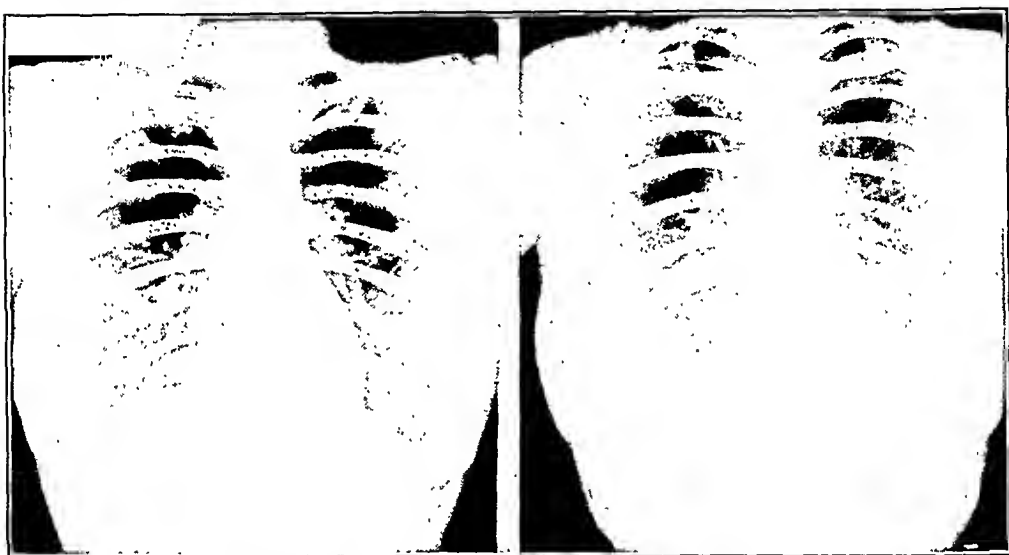


Fig. 1.—Teleoroentgenograms of identical twins (Case 13), showing the close similarity of both the size and the shape of their hearts.

Orthodiasecopy was the radiographic method employed throughout this study. The frontal orthodiagram was made in the usual manner, and the standard methods were employed for determining the various measurements. A planimeter was used to compute the frontal cardiac area. The cardiac volume was estimated by the Rohrer-Kahlstorf formula, which consists of the product of the frontal cardiac area and the horizontal depth diameter of the heart in the lateral position, multiplied by the constant 0.63. We have made the subject of a recent report⁵ an evaluation of this method of determining heart size. The heights of the subjects, without shoes, were measured in centimeters, and their weights in kilograms, with the heavier articles of clothing removed.

DISCUSSION

The tabulated data (Table I) show clearly that there is a striking similarity in the various heart measurements of identical twins. Of great interest are the results in the unrelated subjects (Table II), particularly when it is realized that these pairs of individuals were chosen

TABLE I
IDENTICAL TWINS

NUMBER OF PAIRS	AGE	SEX	WEIGHT (KG.)	HEIGHT (CM.)	TRANSVERSE DIAMETER OF THE HEART (CM.)	DIFFERENCE (CM.)	TRANSVERSE DIAMETER OF THORAX (CM.)	DIFFERENCE (CM.)	CARDIOTHORACIC RATIO (%)	DIFFERENCE (%)	LONG DIAMETER OF THE HEART (CM.)	DIFFERENCE (CM.)	DEPTH DIAMETER IN LATERAL VIEW (CM.)	DIFFERENCE (CM.)	FRONTAL CARDIAC AREA (SQ. CM.)	DIFFERENCE (SQ. CM.)	HEART VOLUME (C.C.)	DIFFERENCE (C.C.)
1	21	F	54 57	154 156	10.2 11.2	1.0	21.2 21.9	0.7	48 51	3	11.7 12.2	0.5	7.4 7.5	0.1	84 86	2	393 405	12
2	21	M	54½ 59	161 159	11.9 12.7	0.8	23.0 23.5	0.5	52 54	2	13.6 13.1	0.5	9.1 9.3	0.2	113 108	5	646 625	21
3	27	F	67 64	170 169	11.4 11.7	0.3	24.0 24.3	0.3	48 48	0	12.3 12.7	0.4	8.2 8.7	0.5	92 89	3	474 490	16
4	34	M	70½ 70½	179½ 179½	13.1 11.9	1.2	27.3 26.7	0.6	48 45	3	13.8 13.0	0.8	9.0 9.1	0.1	111 103	8	629 588	41
5	22	F	54½ 54	162½ 165	11.1 10.5	0.6	23.0 22.8	0.2	48 46	2	12.8 12.3	0.5	8.6 8.8	0.2	97 89	8	526 491	35
6	21	F	54 56	155 157½	10.2 11.2	1.0	20.0 23.7	3.7	51 47	4	11.2 11.5	0.3	8.2 8.9	0.7	80 83	3	414 463	49
7	21	F	51 54½	165 165	8.8 9.0	0.2	22.0 22.1	0.1	45 43	2	11.0 11.7	0.7	7.8 8.0	0.2	81 75	6	396 379	17
8	20	F	58½ 57½	164 162½	12.1 11.6	0.5	24.2 23.4	0.8	50 50	0	13.0 12.2	0.8	7.6 7.7	0.1	114 102	12	543 493	50

TABLE I—CONT'D

9	21	M	65	170	11.2	0.4	23.5	2.6	47	3	12.8	0.4	7.8	0.1	104	6	513	34
			67	175	11.6		26.1		44		13.2		7.9		110		547	
10	21	M	70½	179	11.7	0.2	25.8	0.4	45	2	13.6	0	9.8	0.1	105	4	650	32
			70½	179½	11.9		25.4		47		13.6		9.9		109		682	
11	22	F	50	161	9.4	0.1	20.7	0.2	45	1	11.7	0.2	7.7	0.1	83	1	403	11
			49½	157½	9.5		20.5		46		11.5		7.8		84		414	
12	32	F	59½	165	11.3	1.0	22.8	1.8	50	0	12.5	0.5	8.5	0.9	98	6	524	26
			67½	164½	12.3		24.6		50		13.0		7.6		104		498	
13	22	F	61½	160	10.7	0.3	23.5	0.5	46	2	12.3	0.4	8.5	0.3	89	1	476	12
			63½	160	11.0		23.0		48		12.7		8.2		90		464	
14	19	F	59	167½	11.9	0.7	24.5	1.0	49	1	13.3	0.1	7.7	0.3	107	2	519	9
			57	167½	11.2		23.5		48		13.4		8.0		105		528	
15	26	F	43½	151	9.4	0	20.0	0.2	47	0	11.4	0.1	7.3	0.8	77	7	356	75
			40½	150	9.4		20.2		47		11.5		8.1		84		431	
16	19	F	57½	161	10.4	1.0	22.1	1.4	47	3	12.6	0.4	8.2	0.7	92	1	472	35
			60½	161	11.4		23.5		50		13.0		8.9		91		507	
17	21	F	49½	153	11.3	0.1	25.0	1.0	45	3	12.4	0	8.5	0.3	90	2	483	10
			51	151½	11.4		24.0		48		12.4		8.2		92		473	
18	35	F	64	165	10.7	0.3	22.3	0.3	48	1	12.6	0.5	8.4	0.3	94	1	492	10
			61½	162½	10.4		22.0		47		12.1		8.1		95		482	
19	19	F	68	167	14.0	0.4	26.5	1.0	53	0	14.8	1.2	9.4	0.2	124	6	734	53
			64	167	13.6		25.5		53		13.6		9.2		118		681	
20	41	F	55½	167	10.6	0.1	23.2	1.3	46	3	11.1	0.6	9.1	0.4	83	3	478	5
			54	167	10.5		24.5		43		11.7		8.7		86		473	
Average						0.5		0.9		1.8		0.45		0.33		4.4		27.7

TABLE II
UNRELATED INDIVIDUALS

NUMBER OF PAIRS	AGE	SEX	WEIGHT (KG.)	HEIGHT (CM.)	TRANSVERSE DIAMETER OF THE HEART (CM.)	DIFFERENCE (CM.)	TRANSVERSE DIAMETER OF CHEST (CM.)	DIFFERENCE (CM.)	CARDIOTHORACIC RATIO (%)	DIFFERENCE (%)	LONG DIAMETER OF THE HEART (CM.)	DIFFERENCE (CM.)	DEPTH DIAMETER IN LATERAL VIEW (CM.)	DIFFERENCE (CM.)	FRONTAL CARDIAC AREA (SQ. CM.)	DIFFERENCE (SQ. CM.)	HEART VOLUME (C.C.)	DIFFERENCE (C.C.)
1	21	F	54	154	10.2	0	21.2	1.0	48	3	11.7	0.5	7.4	0.8	84	4	393	21
	21	F	54	155	10.2	0	20.2	1.0	51	3	11.2	0.5	8.2	0.8	80	4	414	21
2	22	F	54	165	10.5	1.5	22.8	1.7	46	3	12.3	0.6	8.8	0.8	89	14	461	112
	22	F	54½	165	9.0	1.5	21.1	1.7	43	3	11.7	0.2	8.0	0.8	75	6	379	21
3	34	M	70½	179½	13.1	1.4	27.3	1.5	48	3	13.8	0.2	9.0	0.8	111	3	629	58
	21	M	70½	179	11.7	1.4	25.8	1.5	45	3	13.6	0.2	9.8	0.8	105	3	650	21
4	21	F	57	156	11.2	0	21.9	1.8	51	4	12.2	0.7	7.5	1.4	86	3	405	58
	21	F	56	157½	11.2	0	23.7	1.8	47	4	11.5	0.7	8.9	1.4	83	3	463	58
5	20	F	58½	164	12.1	0.8	24.2	1.4	50	0	13.0	0.5	7.6	0.9	114	16	543	19
	32	F	59½	165	11.3	0.8	22.8	1.4	50	0	12.5	0.5	8.5	0.9	98	16	524	19
6	50	F	50½	160	10.6	1.2	23.4	2.7	45	0	12.0	0.3	7.0	0.7	86	3	378	25
	22	F	50	161	9.4	1.2	20.7	2.7	45	0	11.7	0.3	7.7	0.7	83	3	403	25

TABLE II—CONT'D

7	48 35	F F	63½ 64	165 165	11.5 10.7	0.8	20.7 22.4	1.7	51 48	3	12.4 12.6	0.2	7.6 8.4	0.8	89 95	6	426 482	56
8	45 45	M M	71 71	163½ 163½	11.6 12.2	0.6	26.1 23.0	3.1	44 53	9	12.4 12.3	0.1	10.3 11.1	0.8	87 99	12	566 694	128
9	21 34	M M	70½ 70½	179½ 179½	11.9 13.1	1.2	25.4 27.3	1.9	47 48	1	13.6 13.8	0.2	9.9 9.0	0.9	109 111	2	682 629	53
10	45 43	M M	70½ 71½	169½ 168½	12.2 12.7	0.5	25.0 25.0	0	49 51	2	12.4 13.5	1.1	9.6 8.4	1.2	97 113	16	587 599	12
11	37 22	F F	50 50	162½ 161	10.4 9.4	1.0	21.8 20.7	1.1	43 45	2	12.4 11.7	0.7	8.1 7.7	0.4	78 83	5	395 403	8
12	17 21	F F	54 54	159 160	10.1 10.3	0.2	22.8 21.8	1.0	49 47	2	11.5 13.0	1.5	7.3 8.2	0.9	81 98	17	372 505	133
13	21 21	M M	64 64	176 176	11.5 12.5	1.0	26.0 25.3	0.7	44 49	5	14.3 14.3	0	8.8 8.5	0.3	122 119	3	674 634	40
14	22 40	M M	67 67½	168 169½	12.9 13.1	0.2	25.9 28.5	2.6	50 46	4	12.9 13.2	0.3	9.5 9.7	0.2	101 115	14	602 700	98
15	44 45	M M	63½ 62	172 172½	13.2 11.1	2.1	24.3 27.0	2.7	54 41	13	14.5 12.7	1.8	9.4 9.2	0.2	117 97	20	690 563	127
Average						0.83		1.7		3.6		0.58		0.74		9.4		60.7

only on the basis of corresponding height, weight, and sex. Table III summarizes the significant data given in Tables I and II.

As pointed out above, in spite of similar height and weight, the general body build in unrelated individuals will vary considerably more than in identical twins, due to constitutional and racial differences in body structure. In this connection it is interesting to note that the greatest variation in the measurements occurred in the internal diameter of the thorax in the unrelated individuals. This is taken to indicate that in this group there actually existed a definite and appreciable difference in body build of the pairs in spite of similar height and weight. Considering this factor we feel that even the heart size of these pairs of unrelated individuals showed an amazing degree of similarity.

TABLE III

AVERAGE OF DIFFERENCES BETWEEN CARDIAC MEASUREMENTS OF PAIRS OF IDENTICAL TWINS AND PAIRS OF UNRELATED INDIVIDUALS OF THE SAME SEX WITH SIMILAR BODY HEIGHT AND WEIGHT

SUBJECTS	TRANSVERSE DIAMETER OF HEART (CM.)	TRANSVERSE DIAMETER OF CHEST (CM.)	CARDIOTHORACIC RATIO (%)	LONG DIAMETER OF HEART (CM.)	DEPTH DIAMETER OF HEART (CM.)	FRONTAL AREA (SQ. CM.)	HEART VOLUME (C.C.)
Identical twins	0.5	0.9	2	0.5	0.3	4	28
Unrelated individuals	0.8	1.7	4	0.6	0.7	9	61

We feel justified, therefore, in concluding that, although individual somatic measurements correlate to a varying degree with heart size, the highest degree of correlation will be found when the various body measurements are considered in the composite form of body build. Further, we believe that the influence of genetic, racial, and environmental factors on the heart is principally through their effect on body structure, of which all organs, including the heart, are integral parts.

SUMMARY AND CONCLUSIONS

1. The heart size as determined by several orthodiaseopic measurements was investigated in twenty pairs of identical twins and in fifteen pairs of unrelated individuals of the same sex with similar body height and weight.

2. The data show a close correspondence of heart size in the identical twins. In the pairs of unrelated individuals the similarity in the heart measurements, although less marked, is rather close, particularly when constitutional and racial differences in body structure which are not brought out by height and weight alone are considered.

3. The conclusion is reached that heart size in normal individuals is dependent principally on body build, and that genetic, racial, and environmental factors are usually important chiefly as they affect body structure. The combination of height and weight, although the best index of body build which exists at present, is not completely satisfactory. We hope that anthropometric studies may produce a more reliable index for expressing body build and thereby offer a more satisfactory measurement to correlate with heart size.

REFERENCES

1. Roesler, H.: Clinical Roentgenology of the Cardiovascular System, Springfield, Ill., 1937, Charles Thomas.
2. Von Verschuër, O., and Zipperlen, V.: Die erb- und umweltbedingte Variabilität der Herzform, *Ztschr. f. klin. Med.* 112: 69, 1930.
3. Gurewitsch, J. B.: Die Rolle der Vererbung und der Umwelt in der Variabilität der Herzgrösse. Untersuchungen an 193 Zwillingspaaren, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 54: 62, 1936.
4. Weitz, W.: Studien an eineiigen Zwillingen, *Ztschr. f. klin. Med.* 101: 115, 1925.
5. Comeau, W. J., and White, P. D.: An Evaluation of Heart Volume Determinations by the Rohrer-Kahlstorf Formula as a Clinical Method of Measuring Heart Size, *Am. HEART J.* 17: 158, 1939.

Department of Clinical Reports

THROMBOANGIITIS OBLITERANS IN A DIABETIC

WILLIAM S. COLLENS, M.D., AND NATHAN D. WILENSKY, M.D.
BROOKLYN, N. Y.

WE HAVE had occasion to observe that clinicians frequently loosely employ the term "endarteritis" to describe most cases of obliterative peripheral arterial disease. Because of this laxity in terminology, the peripheral circulatory impairment in diabetes has often been called "endarteritis obliterans."

We are prompted to present this report in order to stress the importance of greater clarity and accuracy in the clinical differentiation of organic obliterative disease of inflammatory and degenerative or arteriosclerotic origin. It must be remembered that the term "endarteritis" should signify the existence of an inflammatory process in the intima of an artery. The most common inflammatory disease encountered is thromboangiitis obliterans. Other conditions that produce arteritis are tuberculosis, syphilis, pneumonia, rheumatic fever, typhus fever, typhoid fever, and periarteritis nodosa.

The outstanding type of arterial impairment which occurs in diabetes is the degenerative form known as arteriosclerosis obliterans. Its earmarks are degenerative changes in the intima and the media, which assume a fairly definite pattern. Winternitz and his co-workers¹ have recently published a most significant monograph on this subject. They present evidence to show that the degenerative lesion which eventuates in the reduction of the lumen of a major artery arises from hemorrhage from the vasa vasorum into the intima or media. This hemorrhage is then followed by a reaction characterized by an increase in the vascularity of the wall of the vessel, hyaline degeneration in the area of the hemorrhage and, finally, fibrosis and calcification. A cross-sectional study of the artery will usually show the pathologic changes just described, with so much thickening of the wall of the vessel as to encroach upon the lumen.

The presence of thromboangiitis obliterans as a causative factor in impairment of arterial flow in diabetes is an extremely rare phenomenon. A search of the literature has disclosed three reports, including only six cases, of which four can be accepted as authentic.^{2, 3, 4} In order to establish beyond question a diagnosis of thromboangiitis obliterans in a diabetic, it is necessary to possess clinical data which are pathognomonic or, better still, histologic evidence. The presence of peripheral cir-

From the Diabetic Clinic and Department of Medicine, Israel Zion Hospital.
Received for publication Oct. 2, 1938.

culatory impairment in a diabetic usually means arteriosclerosis unless proved otherwise.

We have just encountered a case of a diabetic with peripheral vascular disease and gangrene of a foot in which histologic study of the arteries disclosed the existence of thromboangiitis obliterans. The extreme rarity of the combination of diseases prompts us to present this case.

CASE REPORT

S. I., 42 years of age, an Italian Jew and a rabbi by profession, first came under observation Sept. 23, 1937. He complained of burning pain in both feet for a period of five years. He also had intermittent claudication which had become progressively worse, so that at the time of admission to the hospital he experienced a cramp in his calf muscles on walking 200 feet. He also complained of rest pain and found some relief by hanging his legs over the side of the bed. During this five-year period he had been treated with hypertonic salt solution intravenously and diathermy and had ceased smoking. He had formerly smoked thirty-five cigarettes a day.

Examination on admission disclosed evidence of marked impairment of the blood supply of both legs, worse on the right than the left. No pulsations were palpable in the dorsalis pedis, posterior tibial, and popliteal arteries of the right leg. The left dorsalis pedis pulsation was feeble. There was a small ulcer on the dorsal surface of the right small toe. The Buerger test was positive, more so on the right than the left.

Oscillometric readings were as follows: Above knee—right, 0, left, $\frac{1}{2}$; below knee—right, 0, left, trace; at ankle—right, 0, left, 0; dorsalis pedis—right, 0, left, 0.

The venous filling time⁵ was fifty seconds in the right foot and thirty-four seconds in the left.

During his stay in the hospital it was discovered that the patient had diabetes. On one occasion the sugar content of the urine was 4 per cent. His fasting blood sugar was 238 mg. per cent. The nonprotein nitrogen content of the blood was normal. The blood Wassermann reaction was negative. The blood pressure was 170/110. Roentgenologic studies of his extremities failed to disclose any calcification of his arteries. The electrocardiogram showed left axis deviation and was otherwise normal. The glucose tolerance test disclosed a typical diabetic curve.

These findings were indicative of extensive interruption in peripheral arterial flow, more especially in the right leg. Clinically, one was justified in making a diagnosis of arteriosclerosis obliterans. The absence of calcium deposits, as shown roentgenologically, left the diagnosis somewhat in doubt, for such extensive circulatory impairment is almost always accompanied by such deposits in the walls of the arteries. His diabetes was adequately controlled with a diet containing 250 gm. of available glucose, together with 30 units of insulin daily. Local conservative therapy failed to relieve the patient of pain and the gangrenous ulcer became progressively larger. He left the hospital Oct. 25, 1937, and was admitted to the St. Luke's Hospital November 23, where a mid-thigh amputation of his right leg was performed. The operative wound healed by primary union. The following are the microscopic findings, which Dr. Leila Knox, the pathologist, was kind enough to send us.

"Sections through the popliteal artery show the medial coat free of calcification and only a little sclerotic. Some new blood vessels penetrate throughout the muscle. Occupying the lumen and attached to the intimal coat is a large amount of hyaline thrombus. One portion of its base is invaded by giant cells of the foreign-body type, some containing fat droplets, fibroblasts, and mononuclear cells. Other areas show the lumen completely obliterated by old hyalinized connective



Fig. 1.—Section of popliteal artery showing inflammatory infiltration of intima. Hyaline degeneration and fibrosis of intima are seen in the upper left-hand portion of the photograph (magnification $\times 125$).

tissue and a few recanalized vessels. Portions of the fibrous tissue contain calcium salts. Sections of the anterior and posterior tibial and dorsalis pedis arteries show the lumen free and their walls for the most part very slightly altered. Rarely a vessel shows some calcium infiltration in its media. Some of the nerve fibers show degenerative changes with round cell infiltration (Figs. 1 and 2).

“The diagnosis, based upon the histologic study, is thromboangiitis obliterans.”

DISCUSSION

A clinical diagnosis of thromboangiitis obliterans can be made only in the presence of certain adequate criteria, which include evidence of peripheral circulatory impairment in an adult under the age of 40 years, a history of migrating phlebitis, and the absence of calcification of the vessels. It is not absolutely essential that migrating phlebitis be present. Its association with the disease, however, is pathognomonic of thromboangiitis obliterans. On the other hand, if the patient is a diabetic past the age of 40 years, if hypertension is present and there are calcium deposits in the arterial walls, the diagnosis of arteriosclerosis obliterans cannot be doubted.

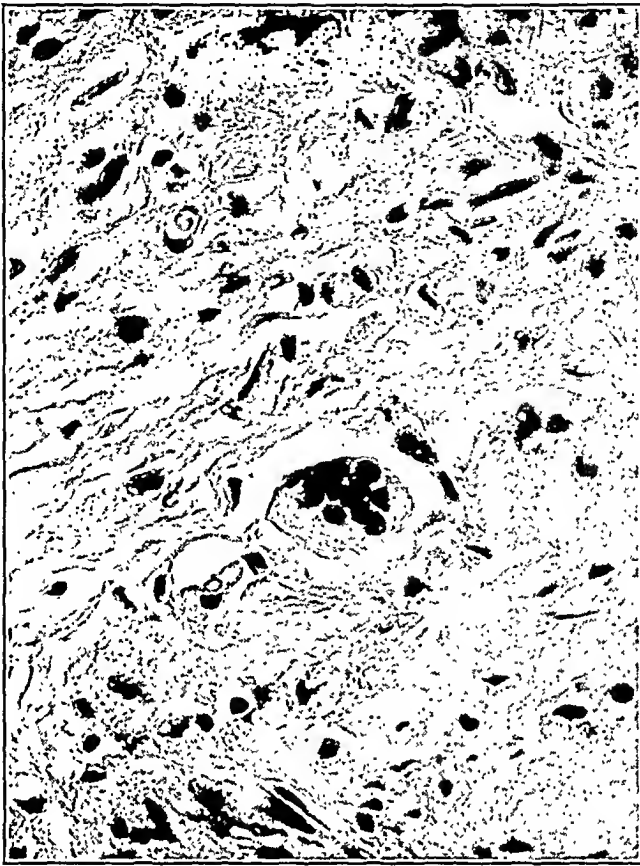


Fig. 2.—High-power view of inflammatory lesion showing foreign body giant cell, fibroblasts, and mononuclear cells (magnification $\times 800$).

In the case which we have reported an absolute diagnosis could not be made on the clinical manifestations alone. Although the patient was a diabetic and had hypertension, the fact that his peripheral arteries could not be visualized roentgenologically and that the arterial blood supply of his legs had been impaired since he was 37 years of age suggested that the peripheral vascular disorder was not of arteriosclerotic origin. It remained for the histologic examination of his major vessels to finally establish the fact that in addition to a mild degree of arteriosclerosis the patient suffered from thromboangiitis obliterans.

SUMMARY

A case of thromboangiitis obliterans in a diabetic is reported. This is a very rare occurrence.

REFERENCES

1. Winternitz, M. C., Thomas, R. M., and Lecompte, P. M.: *The Biology of Arteriosclerosis*, Springfield, Ill., 1938, Charles C. Thomas.
2. Adams, S. F.: A Case of Diabetes Mellitus With Thromboangiitis Obliterans, *Med. Clin. North America* 14: 581, 1930.
3. Davidson, H. J.: Diabetes Mellitus and Thromboangiitis Obliterans in the Same Patient, *J. M. Soc. New Jersey*, 28: 570, 1931.
4. Horton, B. T., and Allan, F. N.: Thromboangiitis of Patients With Diabetes, *Ann. Int. Med.*, 7: 799, 1934.
5. Collens, W. S., and Wilensky, N. D.: Two Quantitative Tests of Peripheral Vascular Obstruction, *Am. J. Surg.* 34: 71, 1936.

COARCTATION OF THE AORTA WITH ASSOCIATED STENOSIS OF THE RIGHT SUBCLAVIAN ARTERY

WILLIAM S. LOVE, JR., M.D., AND JOSEPH H. HOLMS, M.D.
BALTIMORE, MD.

KING¹ has recently reviewed the blood pressure readings in 170 reported cases of coarctation of the aorta, and has added five more cases to the literature of this subject. There were only ten cases in which a significant disparity of pressure in the two arms was present, and, of these ten patients, nine had a higher pressure in the right arm than in the left, possibly due to involvement of the isthmus of the aorta and the mouth of the left subclavian in the same fibrotic anomaly—an explanation offered by Parkes-Weber and Knop,² who quote D. E. Bedford's description of such an instance. East³ reported one case in which the blood pressure in the left arm was found to be 195/145 and that in the right arm, 135/100. No autopsy examination of this patient was made. However, in a second case, upon which clinical observations were not available, autopsy revealed stenosis of the isthmus of the aorta and an anomalous origin of the right subclavian which might have resulted in interference to the circulation of the right arm. He suggests that some such anomaly as this might have been the explanation of the lower blood pressure observed in the right arm in the first case. We wish to report the following case, in which the same type of inequality of the pressures in the two arms was present, and for which peculiarity an adequate cause was discovered.

REPORT OF CASE

A colored man, 44 years old, was admitted to one of the hospitals of Baltimore, Oct. 17, 1932. He complained of a sore throat and an ulcer in the roof of the mouth. Water came through his nose whenever he drank. There had been a penile lesion at the age of 18 years, and the patient admitted having had three or four gonorrheal infections. There were no subjective symptoms of cardiovascular disease.

Physical examination revealed a well-developed and well-nourished colored man. The pupils reacted normally. There was a perforating ulcer of the posterior portion of the hard palate; it entered the left nasal cavity. Several small lymph nodes were palpable in the left posterior triangle of the neck. No abnormalities were noted on examination of the lungs. Marked pulsation of the left carotid, and pulsation both above and below the left clavicle, were readily detected. There was a strong pulsation in the suprasternal notch, and the examining physician felt that there was a mass at this location. The heart was reported to be enlarged to the left, and a loud systolic murmur was heard over the entire precordium,

From the Department of Medicine, University of Maryland.
Received for publication Oct. 18, 1938.

but was maximal at the apex. The pulse rate was 92 and the pulse was said to be noticeably stronger in the left arm. The blood pressure was 210/95 in the left arm, and 150/90 in the right arm. Other findings were essentially negative. A diagnosis of probable syphilitic ulceration of the hard palate and aneurysm of the aorta was made.

Nothing is known of this patient's subsequent course until he was readmitted to the same hospital and died there of bronchopneumonia in June, 1935. The diagnosis was changed to carcinoma of the hard palate during this admission.

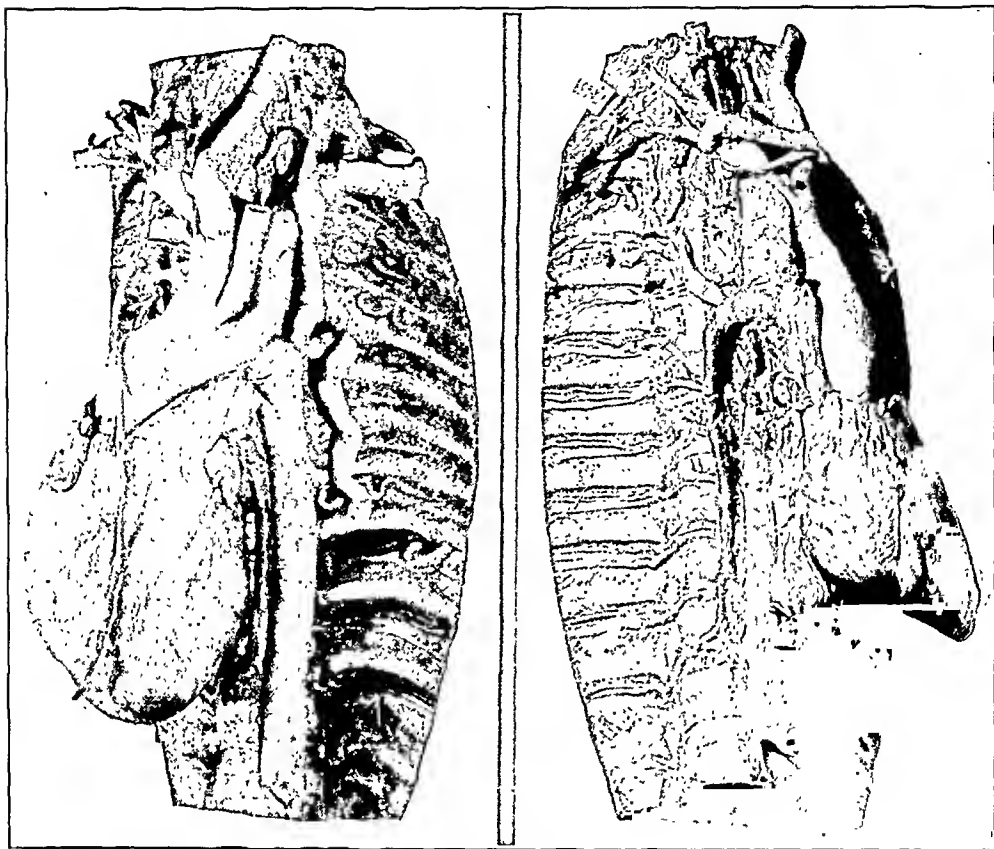


Fig. 1.

Fig. 2.

Fig. 1.—The heart has been moved to the right. The innominate and left common carotid arteries arise from a short trunk. The right subclavian artery is markedly stenosed at its point of origin. The right internal mammary artery is placed across the heart so that it may be compared with the very much larger and more tortuous artery on the left. The ligamentum arteriosum is readily seen extending from the pulmonary artery to the stenosis at the isthmus of the aorta. There is a knoblike dilatation of the aorta just distal to the coarctation. The dilated and tortuous left intercostal arteries are striking, and there has been considerable erosion of the ribs.

Fig. 2.—In this view the heart has been reflected to the left. A single large arterial trunk arising from the aorta below the site of coarctation courses upward and to the right, and in this illustration appears from behind the azygos vein. From this artery arise the second, third, and fourth right intercostals. The second intercostal anastomoses with the right superior intercostal, and two other anastomosing branches arise from the anomalous trunk. The arterial flow to the right subclavian distal to the point of stenosis takes place through these channels. The right intercostals are only slightly dilated and tortuous from the fourth down. The artery (X) seen looping in front of the vertebrae is a tortuous branch of the left thyrocervical trunk which anastomoses with the second intercostal on the left.

No autopsy was obtained. However, the body was assigned to the Anatomy Department of the University of Maryland, where one of us was asked to see it because of an anomalous aorta. The above history was then obtained.

Description of Specimen.—The anatomical findings to which we especially wish to call attention were as follows: The left common carotid and the innominate

arteries took origin from a common trunk. The right subclavian arose from the innominate and at its point of origin was not wider than several millimeters. It reached its maximum width at the vicinity of the origin of the inferior thyroid and internal mammary arteries and the cervico-acromial trunk. A large artery, arising from the arch of the aorta, gave origin to the second, third, and fourth intercostals on the right. The second intercostal anastomosed with the right superior intercostal, which was a branch of the costocervical artery; this last vessel arose from the subclavian distal to the point of stenosis. Doubtless the greater part of the arterial flow to the subclavian artery distal to the stenosis took place through this channel. On the right side all of the arteries that customarily play a role in the collateral circulation of isthmus stenosis were much smaller than those on the left.



Fig. 3.—This illustration displays the extreme tortuosity of the left intercostal arteries, and the resulting erosion and notching of the ribs. The origin of the innominate and left common carotid arteries from a short trunk is shown. This anomaly doubtless was responsible for the clinical impression of a pulsating mass below the suprasternal notch.

Coarctation of the aorta was obvious, and there was a knoblike dilatation of the thoracic aorta just below the site of stenosis. The tremendously dilated and tortuous intercostals, internal mammary, and other vessels playing a role in the

collateral circulation on the left side were striking. Except for the anomalies described above, the collateral circulation developed in this case did not differ in any important detail from that which usually occurs in coarctation of the aorta.

CONCLUSION

We have described a case of coarctation of the aorta in which the very unusual finding of a much lower blood pressure in the right arm than in the left was present. An associated stenosis of the right subelavian artery offered an adequate explanation for this clinical observation. So far as we have been able to ascertain, this is the first case of this type reported in the literature.

REFERENCES

1. King, John T.: The Blood Pressure in Stenosis at the Isthmus of the Aorta, *Ann. Int. Med.* 10: 1802, 1937.
2. Parkes-Weber, F., and Knop, F.: Stenosis of the Aortic Isthmus, With Subcutaneous Pulsating Arteries on the Back, *Med. Press and Circ.* 127: 195, 1929.
3. East, T.: Coarctation of the Aorta, *Proc. Roy. Soc. Med.* 25: 796, 1932.

Department of Reviews and Abstracts

Selected Abstracts

Fry, William E., and Swanson, Edward E.: Digitalis Assay by the Cat Method Under "Sodium Amytal" Anesthesia. *J. Am. Pharm. A.* 28: 309, 1938.

As anesthetics, in the assay of digitalis by the cat method, two short-acting barbituric acid derivatives were compared with ether.

When the cats were anesthetized with the barbituric acid compounds, it required more digitalis to kill than with ether.

The size of the cat unit for digitalis varies with the anesthetic agent used.

AUTHORS.

Johnson, J. Raymond, and Di Palma, Joseph R.: Intramyocardial Pressure and Its Relations to Aortic Blood Pressure. *Am. J. Physiol.* 125: 234, 1939.

A method of optical recording is described for measuring directly the extent of the intramyocardial pressure at any desired depth in the wall of the left ventricle, and the contour of such pressure curves is described. By means of simultaneous records of the pressure from the ventricular wall and from the aorta the following important relations are found to obtain:

1. During the height of systole there exists in the wall of the ventricle a gradient of pressure decreasing from the deeper to the more superficial layers.

2. In the depth of the myocardium this pressure is always greater than aortic pressure but in the superficial layers it may be equal to or even less than the pressure in the aorta and coronary arteries.

These results indicate that while the deeper coronary vessels must become completely occluded during the height of cardiac contraction there may be a continuous forward movement of blood in the more superficial layers of the myocardium.

AUTHORS.

Brüner, H., and Mertens, W.: Experimental Changes in Blood Volume I. Blood Pressure and Pulse Rate Following Bleeding. *Arch. f. Kreislaufforsch.* 3: 223, 1938.

Studies were carried out on twenty-four dogs in whom venous hemorrhages were produced. The effect of hemorrhage was compared in some animals before and after denervating the reflex buffer nerve mechanism (carotid sinus and aortic end organ areas). The buffering nerve mechanism was found able to cope, as far as blood pressure is concerned, with a loss of as much as 20 per cent of the blood volume. With each further loss of blood up to 40 per cent of the blood volume, the effect on blood pressure became greater. Beyond 40 per cent the further loss of blood had less effect on blood pressure. The lowest point attained by the blood pressure is 35 to 45. The pulse rate increases progressively with hemorrhage and reaches its maximum when the blood pressure reaches its lowest level.

In the animal with denervated buffer nerve mechanisms, the blood pressure fall is progressive in successive hemorrhages and reaches its low point of 35 to 45. The initially rapid heart rate is not changed significantly.

The amount of blood which can be lost before the nerve buffering mechanism fails is dependent on the initial blood pressure.

KATZ.

Eckey, P., and Vorwerk, W.: The Effect of Strophanthin on the Gaseous Metabolism and Heart Minute Volume in the Presence and in the Absence of Buffer Receptors. *Arch. f. Kreislaufforsch.* 3: 235, 1938.

Fifteen dogs were used and anesthetized with urethane. The effect of intravenous strophanthin was observed before and after denervating the buffer receptors (carotid sinus and aortic areas). In animals with the buffer nerves intact, the minute volume decreases following strophanthin. At the same time the oxygen consumption and blood pressure were unchanged. In animals with the buffer receptors denervated, the minute volume of the heart, the blood pressure and the oxygen consumption increased.

On the basis of these results, the authors postulate the possibility that the difference in action of strophanthin in normal and failing hearts might be due to a loss of buffering nerve receptor activity.

KATZ.

Meyer, F.: A Manometer With Photoelectric Registration (Air Bubble Manometer). *Ztschr. f. Kreislaufforsch.* 30: 734, 1938.

A blood pressure manometer is described briefly. This consists of a horizontal tube with a gas bubble in it so situated as to be interposed between a light source and a photoelectric cell. The size of the gas bubble varies with the pressure in the manometer and so alters the amount of light permitted through. This is recorded by the photoelectric cell. When calibrated, the pressure values can be determined.

KATZ.

Griffith, J. O., Zinn, C. J., and Comroe, B. I.: Effect of Sympathectomy on the Vasa Vasorum of the Rat. *Arch. Path.* 26: 984, 1938.

While it may be assumed that the vasa vasorum share in the general response of blood vessels to sympathectomy, this has never been demonstrated. By injecting particulate matter into the circulation of rats in which bilateral lumbar sympathectomy had been performed and into normal rats, the authors have found that the number of vasa vasorum in the femoral artery of the rat is increased five days after lumbar sympathectomy.

NAIDE.

Cottenot, P., and Heim de Balsac, R.: Experimental Anatomical-Radiological Study of the Circulatory System of the Normal Newborn Infant by Post-Mortem Shadows. *Gynéc. et obst.* 35: 251, 1938.

Post-mortem injections of the various chambers of the heart in eight stillborn children, showed the position of the ventricles relatively more anterior in relation to the auricles than in the adult. The whole heart is more globular and larger in proportion to the thorax. The left auricle (lying posteriorly) and the right ventricle (lying anteriorly) have relatively small volume; this is explained by the inactive state of the pulmonary circulation. For the same reason the pulmonary vessels also are poorly developed. The aortic arch is entirely to the front and to the left of the midline, and the ascending and descending limbs of the arch are seen side by side rather than behind each other. The trunk of the pulmonary

artery is in striking contrast to the branches which are quite small, while the trunk is continuous with the ductus arteriosus. This creates an x-ray shadow very similar to that of persistent ductus arteriosus in the adult.

JENSEN.

Burch, George E., and Sodeman, William A.: A Direct Method for the Determination of Venous Pressure; Relationship of Tissue Pressure to Venous Pressure. *J. Clin. Investigation* 18: 31, 1939.

The application of the tissue pressure apparatus to the direct determination of venous pressure was highly satisfactory and disclosed definite advantages.

Comparison of indirect and direct determinations of venous pressure on the same vessel indicates that the former are in error by approximately the tissue pressure. This factor becomes increasingly important as the venous pressure decreases.

AUTHORS.

Hollmann, H. E., and Hollmann, W.: The Einthoven Triangle Compared With Other Lead Combinations. *Arch. f. Kreislaufforsch.* 3: 191, 1938.

The first section deals with the mathematical and graphic solution of Einthoven's formulations. It is restated that formula $\text{Lead II} = \text{Lead I} + \text{Lead III}$ applies to any triangle, not only to the equilateral one. As for the geometric aspects of the Einthoven triangle, there are definite limits in applying it actually because of eccentricity of the heart and nonhomogeneity of the body field.

In the second section the author used four schemes to get the vectorgram (record of the resultant vector during the heart cycle inscribed as a standing wave on a cathode ray oscillograph), two of which are rather elaborate; the others were chest triangle and the limb triangle respectively. These were all similar.

KATZ.

Grosse, F.: Electrocardiographic Findings in Cardiac Infarctions With Various Chest Leads. *Arch. f. Kreislaufforsch.* 3: 245, 1938.

This is a study based on nineteen patients, of whom sixteen had anterior, eight had posterior, and five had combined anterior and posterior infarcts. The author correlated clinical and electrocardiographic findings. The value of chest leads is emphasized especially when the limb leads are atypical. An M-shaped QRS and an elevated S-T segment were found at autopsy to have occurred in a patient with combined infarction. In determining prognosis the clinical and not the electrocardiographic findings are important.

KATZ.

Levy, Robert L., Bruenn, Howard G., and Russell, Nelson G., Jr.: The Use of Electrocardiographic Changes Caused by Induced Anoxemia as a Test for Coronary Insufficiency. *Am. J. M. Sc.* 197: 241, 1939.

A method has been described for inducing generalized anoxemia without rebreathing: employing an apparatus which enables the subject to breathe a mixture of 10 per cent oxygen and 90 per cent nitrogen at the normal rate of pulmonary ventilation.

Changes in the form of the electrocardiogram have been analyzed following the induction of anoxemia in 105 persons, comprising 66 normals, 23 with disease of the coronary arteries, 11 in whom coronary disease was suspected but doubtful, and 5 with severe anemia.

Criteria for normal and abnormal responses have been evolved. It is recognized that the material is relatively small and that the criteria must be regarded as tentative. It has not been possible, thus far, to correlate the clinical diagnoses with the anatomic lesions.

Changes regarded as abnormal have occurred in patients with clinical symptoms and signs of coronary insufficiency. Similar alterations have been observed in those with anemia but without signs of cardiac disease.

There have been no serious untoward effects. Because of two unpleasant reactions, it is suggested that the test should not be given to patients with cardiac insufficiency and should not be repeated in the same patient within twenty-four hours.

Changes in the form of the electrocardiogram caused by induced anoxemia may be used as a clinical test for insufficiency of the coronary circulation, whether this be manifest or latent. An index is afforded of the adequacy of the "coronary reserve." It should be of value in distinguishing pain of coronary origin from pain in the chest due to other causes, as well as from pain referred from the abdomen. It is possible that it can be employed also to study, in man, the effect of drugs and of various surgical procedures on the efficiency of the coronary blood flow. Such studies are in progress.

AUTHORS.

Masshoff, W.: Influence of Diphtheria on the Size of the Heart and on the Heart Muscle Structure. *Arch. f. Kreislaufforsch.* 3: 142, 1938.

This study gives a post-mortem analysis of twenty hearts from patients 1½ to 16 years of age, dying of diphtheria or its complications. Every heart showed an enlargement in one of its chambers. Evidence indicates that heart failure was right sided in these patients, and there was evidence of myocardial degeneration rather uniformly distributed throughout the heart. Inflammatory damage in the heart appears to be a complication.

KATZ.

Lepeschkin, E.: The Normal Chest Electrocardiogram in Childhood. *Arch. f. Kreislaufforsch.* 3: 321, 1938.

This is a study based on fifty normal children of from 2 weeks to 15 years of age utilizing ten to twenty roentgen-controlled combinations of chest electrodes and left leg or right arm electrodes.

The initial complex is diphasic. In infants the first upright phase is larger than the inverted phase on the right of the sternum. In older children this is true over the apex. The difference is attributed to the relative thickness of the two ventricles at these two ages. The T wave is inverted on the right chest anteriorly and upright on the left. On transition a diphasic T is found. This transition is more to the left anteriorly in children than in grown-ups and this deviation from the midline is greater the younger the child. These differences are related to the more lateral position of the interventricular groove, in the younger child. These changes are considered in relation with the regional distribution of the activity.

KATZ.

Keil, Harry: The Rheumatic Subcutaneous Nodules and Simulating Lesions. *Medicine* 17: 261, 1938.

Consideration of the data presented in this monograph seems to point in the direction of the establishment of the following principles:

The term rheumatic nodule should be applied to those lesions occurring in the course of undoubted rheumatic fever. The lesion presents definite characteristics,

the most important being the location, the transiency (relative and absolute), and the relations to the other rheumatic phenomena, notably cardiac involvement. The highest degree of clinical specificity is enjoyed in childhood, and the rheumatic subcutaneous nodule may be said to be highly specific of rheumatic fever in that age group, provided the clinical attributes correspond closely with those mentioned in the text.

The specificity of the rheumatic nodule is dependent on its clinical properties and relations. The combination of pathologic changes found in microscopic examinations, while often suggestive, shows no pathognomonic characteristics and may be simulated by other lesions.

The true rheumatic nodule is practically always associated with clinical evidence of cardiac involvement in one form or another. The evidence compiled in this monograph substantiates the view that disease of the heart is the fundamental hall-mark of rheumatic fever. This may not always be evident clinically, but its occurrence is to be expected at post-mortem examination. When evidence of cardiac involvement in one form or another is completely lacking at necropsy, there is reason to believe that the case was not one of rheumatic fever and the burden of proof rests on those who wish to classify the condition in the rheumatic category. On the other hand, the presence of rheumatic heart disease, particularly if the changes are old and healed, does not necessarily indicate that nodules appearing at the time are inevitably related to the rheumatic process; each case must, therefore, be evaluated critically, and the factor of coincidence must be taken into account. The difficulties inherent in this problem are increased, owing to the lack of uniformity in the pathologic criteria for the recognition of rheumatic fever.

The typical nodule in rheumatoid arthritis differs from that in rheumatic fever in many clinical attributes and in some pathologic respects. The clinical differences appear to be more important than the pathologic differences, the latter still requiring evaluation.

The nodule in rheumatoid arthritis shows greater resemblances to the juxta-articular node in syphilis. This is especially true in a clinical sense and it probably also holds pathologically, if the ordinary methods of staining are used for microscopic study. On the other hand, it is possible that investigations pursued by supravital staining (McEwen) may furnish data of differential diagnostic importance.

The conception of the syphilitic nodule as an entity rests on three features: (1) its association with other manifestations of syphilis; (2) the almost invariable presence of a positive Wassermann reaction; (3) the striking response to anti-syphilitic remedies.

The controversy regarding the relative incidence of subcutaneous lesions in rheumatoid arthritis and in syphilis is clarified by the realization that both varieties of nodules occur, but that their respective incidence will be governed largely by the type of material under observation.

The pathologic criteria for the diagnosis of a "rheumatic nodule" are discussed critically. Evidence is presented to show that these appearances, as observed in the ordinary microscopic examinations, are not pathognomonic of a single disease. How far the supravital studies will provide criteria for the differentiation of the various nodules is still problematic, but it is a method worthy of extended investigation. Caution is advised in drawing etiologic conclusions on the basis of morphologic resemblances.

AUTHOR.

Hadfield, G.: *The Rheumatic Lung*. *Lancet* 2: 710, 1938.

The primary lesion responsible for the consolidation of the "rheumatic lung" is widespread fibrinous alveolitis. This is followed by a cellular infiltration, mono-

nuclear in type, relatively slow in development but eventually becoming copious and diffuse.

In fatal cases this primary lesion is complicated by hyaline pseudomembrane formation in most of the alveolar ducts in the consolidated lung.

As in other varieties of pneumonitis this process takes place in lungs in which the finest ramifications of the airway contain viscid albuminous exudate and after a period of severe inspiratory dyspnea.

The dyspnea which initiates membrane production in the rheumatic lung is probably primarily cardiac in origin.

AUTHOR.

Goormaghtigh, Norbert, and Handovsky, Hans: Effect of Vitamin D₂ (Calciferol) on the Dog. Arch. Path. 26: 1144, 1938.

The authors have made extensive pathologic and pharmacologic studies, extending over a period of three years, of the effect of calciferol (vitamin D₂) on the dog. Observations were centered on the arterioles of the kidney. Moderate daily doses of calciferol caused hypertrophy and morphologic changes indicative of increased cell metabolism in both types of cells in the arteriolar media (the ordinary smooth muscle and the afibrillar cell). The afibrillar cells are identical with the cells found in the glomi or arteriovenous shunts in the skin. Larger but non-lethal doses do not affect the afibrillar cells but cause regressive changes in the smooth muscle cells. Some of these changes are reversible after discontinuation of the treatment. These regressive changes are present to a smaller extent in the arterioles of the spleen, neurohypophysis, thyroid, gonads, adrenal and pancreas. In the normal dog calciferol leaves the aorta macroscopically unchanged. With the dosage employed, alterations of the elastic membrane or intimal reactions are rarely observed. Arteriolar calcinosis is absent. Calciferol in heavy doses causes necrosis of the arteriolar media, a lesion similar to that found in scarlet fever and eclampsia.

In the dog's kidney calciferol causes arteriolonecrosis, with or without nephritis, depending on the dose employed. They offer the following explanation of the pathogenesis of the renal lesion. In hypervitaminized dogs tubular lesions are produced as a result of the profound changes in the chemical make-up of the blood, with marked excretion of calcium. Because of the anatomic connection between the vascular pole of the glomerulus and distal part of the distal convoluted tubule, damage to the tubule causes mechanical irritation of the vas afferens, with vasoconstriction of the arteriole. This vasoconstriction results in glomerular collapse or regression. They stress therefore the significance of the tubular lesions in nephrosclerosis, pointing out that these lesions are responsible for glomerular regression.

Doses of from 50 to 70 micrograms per kilogram cause inversion of the vascular response to epinephrine. Heavier doses increase the sensitivity of the hypertensive response.

Arterial hypertension develops when the treatment is maintained at a dosage of from 100 to 700 micrograms per kilogram per day. Doses not exceeding 250 micrograms per kilogram have a thyrotropic effect.

The significance of these observations in the problem of human arteriosclerosis is discussed.

NAIDE.

Steinert, R.: Hypertension. Does the Mortality Increase in Essential Hypertension? A Statistical Analysis. Ztschr. f. Kreislaufforsch. 30: 693, 1938.

This is an analysis of causes of death of people over 50 from 1925 to 1934. On the basis of the assumption that most cases of apoplectic death are brought about

by essential hypertension, the author concludes that in Norway no increase occurred in the latter in this ten year period since the death rate from apoplexy was unchanged (41/10,000 population). By contrast, death from chronic heart disease 48 per cent in the last five-year period as compared with the first.

KATZ.

Pickering, G. W.: The Problem of High Blood Pressure in Man. *Brit. M. J.* 1: 1, 1939.

The Herzstein Lectures were delivered before the University of California and Stanford University, San Francisco, May 23 to 26, 1938.

The author attempts to develop a line of thought rather than to prove a scientific hypothesis. He discusses the available evidence supporting the theory of a chemical substance formed in the kidney which, when liberated, is fixed in the blood vessels and results in a rise in blood pressure.

McCULLOCH.

Horton, Bayard T.: The Outlook in Thrombo-Angiitis Obliterans. *J. A. M. A.* 111: 2184, 1938.

This is a review of 948 patients with thromboangiitis obliterans. The distribution as to geography, age, sex, and race is discussed. Twenty-one of the patients were women; the remaining 927 were men.

Ninety-three per cent of the total were smokers. A greater percentage of amputations occurred among the smokers than among the nonsmokers.

A study of amputations for periods of three, five, and ten years after the onset of the disease indicates that approximately 70 per cent of patients will go for a period of three years from the onset without the necessity of amputation, whereas only 60 per cent will go for a period of five years and only 40 per cent for a period of ten years without being obliged to undergo amputation.

Early diagnosis and thorough education of the patient concerning the nature of his disease and the care of his extremities are important in preventing amputation.

NAIDE.

Mills, John H., and Horton, Bayard T.: Clinical Aspects of Aneurysm. *Arch. Int. Med.* 62: 949, 1938.

A total of 596 cases of aneurysm were recorded at the Mayo Clinic in the years 1925 to 1935, inclusive. In this series of cases, 143 of the aneurysms were intracranial, 339 were intrathoracic, 80 were intra-abdominal, 21 involved the extremities, and 13 were of a miscellaneous character. The etiology, symptoms, and physical findings of the various types of aneurysms encountered are discussed. Syphilis was present in 3.5 per cent of the cases of intracranial aneurysm, in 70 per cent of the cases of thoracic aneurysm, in 8.8 per cent of the cases of intra-abdominal aneurysm, in 9.5 per cent of the cases of aneurysm of an extremity, and in 7.7 per cent of the miscellaneous cases of aneurysm. In a total of 172, or 28.9 per cent, of the 596 cases, the diagnosis of aneurysm was verified at operation or necropsy.

NAIDE.

Goldbloom, A. Allen, and Lieberman, Abraham: Clinical Studies in Circulatory Adjustments. *Am. J. M. Sc.* 197: 182, 1939.

The factors maintaining circulatory equilibrium, cardiac output, blood volume, venous pressure, blood pressure, and circulation time are defined and discussed.

Historically the importance of cardiodynamic studies in explaining the nature of, and circulatory mechanisms involved in certain clinical conditions; hypertension, central versus peripheral failure, right versus left heart failure, hyperthyroidism, and polycythemia is stressed.

It has been found useful from the diagnostic and therapeutic points of view to group decompensated cardiacs into plus and minus forms of failure, based on blood volume readings.

From the practical viewpoint, the greatest uses made of cardiodynamic studies are in the following:

1. Borderline cases of hyperthyroidism, where an increased cardiac output, increased blood volume and rapid circulation time distinguish this condition from neurocirculatory asthenia or incipient tuberculosis (in which the above values are normal).

2. In polycythemia vera the very high blood volume and hematocrit reading are usually sufficient to distinguish it from the symptomatic polycythemias, which do not yield such high figures.

3. In the differentiation between right and left heart failure, aside from clinical differences, the lengthened arm-to-lung circulation time in right-sided failure is of distinct value. By subtracting the arm-to-lung circulation time from the total pulmonary circulation time (arm-to-head) one can estimate the speed through the left heart circuit.

4. In decompensation, often the very first sign of right heart failure is an increase in the venous pressure.

AUTHORS.

Davis, D.: The Role of Rest and Exercise in Congestive Heart Failure. New England J. Med. 219: 412, 1938.

There is no agreement in the literature as to the length of time patients should rest after evidence of congestive failure has disappeared, or as to the advisability of exercise in convalescence. The historical aspect of these questions is considered.

The question of the advisability of exercise in convalescence is discussed at length. No data were found to support the contention that this therapy improves the capacity of the heart.

The results of prolonged bed rest in eleven cases are compared with those in a control group treated in the accepted manner. The course in these eleven cases was appreciably better than that in the control group.

These results call for a program which will take into consideration an adequate initial period of rest, adequate subsequent reduction in activity, and periodic prophylactic bed rest. Such a program is outlined.

AUTHOR.

Wolferth, Charles C., and Margolies, Alexander: Movements of Roentgen-Opaque Deposits in Heart Valve Areas. Am. J. M. Sc. 197: 197, 1939.

A cardiac roentgenkymogram timed by an electrocardiogram was made in such a way as to demonstrate the movements, toward and away from each other, of the apex and of a calcium deposit in the region of the aortic valve. From the data obtained in this case and four others (three previously published) in which roentgenkymograms were made of calcium deposits in either the mitral valve or aortic valve area, the following points are emphasized.

The change in size and shape of the left ventricle during contraction is probably due more to shortening of the long axis than to movement of the lateral wall.

The floor of the auricle (roof of the ventricle) does not remain in a relatively fixed position as is usually assumed, but is pulled vigorously toward the apex during ventricular systole, while the apex is moving toward the base. The directions of movement are reversed in diastole.

The movements of the left ventricular border are much smaller than the movements of base and apex. The shortening of the long axis may be so great that the left border actually moves outward during the early part of systole. The foregoing facts should be taken into consideration in any attempt to study ventricular contraction by means of recording the movements of the left ventricular wall. These movements may fail to reflect the vigor or extent of the left ventricular contraction.

The marked movement of the auricular floor, as a result of ventricular contraction, must create a powerful suction which is an important factor in bringing about auricular filling.

It is probable that when movements of the external walls of the heart are restricted, the filling and emptying of its chambers are made possible by the effects of ventricular contraction and relaxation on movement of the tissues separating auricles and ventricles.

AUTHOR.

Reid, Mont R., and McGuire, Johnson: Arteriovenous Aneurysms. *Ann. Surg.* 108: 643, 1938.

An analysis of twenty-one cases of arteriovenous and nine cases of cirroid aneurysms is presented, which is supplemented by observations upon experimentally produced arteriovenous aneurysms in dogs.

Sixteen of the arteriovenous aneurysms were operated upon and all of them, except one case of pulsating exophthalmos, were cured. In two instances the aneurysms healed spontaneously without operation. Four patients failed to return for later operations and could never be traced. All of the nine cirroid aneurysms were operated upon; three were cured, and the other six were more or less improved. There were no deaths in the entire series of thirty cases. There was a total of thirty-nine operations upon the twenty-four patients who were subjected to surgical treatment.

Clinical and experimental observations which may throw some light upon the physiologic and pathologic effects of arteriovenous fistulas are discussed in some detail. The principal effects noted and studied were: ten instances of cardiac damage; eleven instances of thinning and dilatation of the proximal artery; circulation time upon six patients; blood volume upon three patients; ten instances of Branham's bradycardic phenomenon; thirteen instances of blood pressure alterations; studies upon the venous blood pressures of nine patients; nine instances of markedly increased collateral circulation; five instances of an increase in the size and length of an extremity; four instances of associated nerve paralyses; two instances of double arteriovenous fistulas; and two instances of spontaneous healing of the aneurysm.

In our limited clinical and experimental observations, we could not confirm Holman's findings of a marked increase of the total circulating blood.

A Venturi meter was used in some of the experiments to measure the flow of blood in a segment of the vena cava. An easy method of making an arteriovenous fistula which can be alternately closed and opened is illustrated.

The time to operate, and the standard curative operative procedures, are discussed. Two new operative procedures are illustrated and described in the case reports.

AUTHORS.

Heumans, C.: Some Aspects of Blood Pressure Regulation and Experimental Arterial Hypertension. *Surgery* 4: 487, 1938.

Experimental investigations have demonstrated that the regulation of blood pressure is essentially and fundamentally an automatic, proprioceptive reflex mechanism. In fact, the endovascular pressure itself regulates automatically the cardiac output, the circulating blood volume, and the peripheral vascular resistance so well that the arterial pressure is maintained within or quickly restored to normal limits. This homeostasis of the arterial pressure is effected mainly by the intermediation of the pressoreceptor innervation of different arterial and venous vascular areas.

The author's experiments suggest that the arterial hypertension induced by renal ischemia may be due to a humoral factor which increases the excitability of the peripheral blood vessels to constrictor stimulations, mainly to the neurogenic vasoconstrictor influences, the same humoral factor inducing, on the other hand, a direct peripheral vasoconstriction and a disturbance in the physiologic mechanisms of the pressoreceptive reflex regulation of blood pressure. The sympathectomy up to the total removal of both ganglionic chains neither prevents nor cures this experimental nephrogenic hypertension.

AUTHOR.

Craig, W. McK.: Essential Hypertension: The Selection of Cases and Results Obtained by Subdiaphragmatic Extensive Sympathectomy. *Surgery* 4: 502, 1938.

The surgical treatment of hypertension, which consists of subdiaphragmatic resection of the major, minor, and lesser splanchnic nerves, celiac ganglion, and lumbar sympathetic ganglions, is associated with a small risk and is followed by satisfactory alleviation of symptoms in selected cases.

Assuming that all hypertension can be divided into four groups, depending upon the severity, Group 1 does not require surgical treatment and Group 4 is too severe and too far advanced to warrant the expectation of adequate results. Groups 2 and 3 then should be considered for operative treatment. More important than the group are the preoperative tests which indicate the potential physiologic changes that will follow sympathetic denervation of the vascular area below the diaphragm.

The so-called test indicates the upper limits of the blood pressure resulting from emotion or cold. The four other tests indicate the lower limits of the blood pressure readings associated with prolonged vasodilatation, and, therefore, denote the probable values for the blood pressure following extensive sympathectomy. They are as follows: (1) Twenty-four consecutive hourly determinations of the blood pressure are made while the patient is in bed, to establish the maximal blood pressure, the minimal blood pressure, and the mean or average blood pressure. (2) Slow and intermittent intravenous injection of a 5 per cent solution of pentothal sodium is made until there is no further drop in blood pressure. (3) One-half grain (0.032 gm.) of sodium nitrite is administered at intervals of thirty minutes until six doses have been given. (4) Hourly determinations of blood pressure are made during rest and sleep for a minimum of twenty-four hours.

If the blood pressure drops to nearly normal and if the patient is less than 50 years of age, the operation should be considered.

The results in a large series of cases have been quite satisfactory. The effect of the operation is physiologic in character, and, if so considered, the results justify the procedure.

AUTHOR.

American Heart Association, Inc.

RADIO CITY

50 WEST 50TH STREET, NEW YORK, N. Y.

DR. WILLIAM D. STROUD
President

DR. PAUL D. WHITE
Vice-President

DR. HOWARD B. SPRAGUE
Secretary

DR. WALTER W. HAMBURGER
Treasurer

BOARD OF DIRECTORS

DR. T. HOMER COFFEN Portland, Ore.
DR. CLARENCE DE LA CHAPELLE New York City
DR. WILLIAM DOCK San Francisco
DR. HUGH FARRIS St. John, N. B., Canada
DR. WALTER W. HAMBURGER Chicago
DR. GEORGE R. HERRMANN Galveston
*DR. EMMET F. HORINE Louisville
DR. T. DUCKETT JONES Boston
*DR. EMANUEL LIBMAN New York City
DR. DREW LUTEN St. Louis
DR. GILBERT MARQUARDT Chicago
*DR. H. M. MARVIN New Haven

*DR. EDWIN P. MAYNARD, JR. Brooklyn
DR. THOMAS M. McMILLAN Philadelphia
DR. JONATHAN MEAKINS Montreal
*DR. FRANKLIN NUZUM Santa Barbara
DR. STEWART R. ROBERTS Atlanta
*DR. ROY W. SCOTT Cleveland
*DR. HOWARD B. SPRAGUE Boston
*DR. WILLIAM D. STROUD Philadelphia
DR. LOUIS VIKO Salt Lake City
*DR. PAUL D. WHITE Boston
DR. FRANK N. WILSON Ann Arbor
*DR. IRVING S. WRIGHT New York City
DR. WALLACE M. YATER Washington, D. C.

DR. H. M. MARVIN, *Chairman, Executive Committee
and Acting Executive Secretary*

GERTRUDE P. WOOD, *Office Secretary*

TELEPHONE CIRCLE 5-8000

THE American Heart Association, sponsor of the first International Health Broadcast, stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is \$5.00 a year and journal membership at \$10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

*Executive Committee.

The American Heart Journal

VOL. 17

JUNE, 1939

No. 6

Original Communications

THE SOUNDS PRODUCED BY THE FRICTION OF NORMAL SEROSAE*

TEÓFILO ORTIZ, M.D.
MEXICO CITY, F. D.

FOR a century, since the pioneer contribution of Laënnec,¹ auscultation has been studied assiduously by physicists, physiologists, and clinicians, yet there are many acoustic phenomena whose significance has not been determined. The cardiac sounds and the adventitious cardiovascular sounds are not yet fully understood and offer, therefore, obvious difficulties in diagnosis.

Empirically, we have succeeded in identifying the clinical significance of many acoustic phenomena, but daily practice demonstrates the insufficient pathogenic value accorded to other phenomena not less frequent or important. Mackenzie² stated correctly, "How little we know of the causation of murmurs," and Wiggers, when dealing with the cardiac sounds, explains the mechanism of the first one merely in terms of probability. The clinical investigators have avoided academic discussions and attempted to establish the value of the acoustic data on the basis of the pathologic findings; but it is frequently impossible to obtain pathologic control, and the necropsy findings often contradict the clinical data. The complexities of the problem are shown by the numberless hypotheses accumulated by clinicians during a hundred years of auscultation; on the other hand, the contemporary literature bears testimony to the hope of finding a definite reason for the disparity between the physical phenomena and the functional evolution. Pathologic physiology may bring certainty to prognosis and therapeutics.

A glance at the appendix of White's book, *Heart Disease*, which includes representative examples of "the more important or puzzling problems in cardiovascular diagnosis," justifies any contribution to the subject.

*From the General Hospital, Mexico City, F. D.
Received for publication Sept. 3, 1938.

The present study deals with the acoustic phenomena which occur when there is friction of two serosae in the pericardium, pleura, or peritoneum. The source of these sounds is really in the membranes or structures covered by endothelium when interserous friction occurs. The purpose of this study was not only to review the classical auscultatory findings in cases of nonglistening, diseased, or inflamed serosae, but also to investigate the possibility of the appearance of sounds in normal serosae lubricated by the physiologic transudates.

Semeiological investigations of this problem have been made frequently since Laënnec. The opinions derived therefrom are practically unanimous: both the older and contemporary clinicians agree that intact serosae are aphonic, or silent. Laënnec himself, however, and several other observers have expressed suspicions that this proposition may have limitations.^{3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13} Some authors have favored the view that minimal lesions of the endothelium or insignificant alterations in their lubrication might be responsible for some of the acoustic phenomena present in apparently healthy individuals. Nevertheless, they did not conclude that perfectly normal serosae, with a physiologic lubrication, can yield acoustic phenomena useful in clinical work. Indeed, such a conclusion cannot be legitimately derived from their experiments or observations because of the lack of adequate controls.

This problem, apparently only speculative in nature, is in reality intimately bound up with the validity of auscultatory data. It may be approached experimentally, and hence supply conclusions of interest especially for cardiologic pathology and semeiology.

METHODS

Normal, healthy cats, rabbits, and dogs were used. This material eliminates, therefore, possible objections as regards the integrity of the serosae. The animals were killed by excessive anesthesia, by hemorrhage, or by asphyxia. Several fragments of the thoracic and abdominal walls and also several viscera (heart, liver, spleen, intestine) were collected.

The lubricating fluids were water, normal saline, Ringer's solution, oxalated or saturated blood, blood plasma or blood serum, and saliva, all from the same animal. The normal transudates from the serosae might also be employed; it is difficult, however, to collect them. The inevitable evaporation which occurs renders the serosae sticky; it was therefore invariably necessary to employ the other lubricating agents mentioned. Furthermore, the handling of the pieces during their preparation might leave microscopic foreign bodies on the endothelium. For this reason, all the structures employed were always washed first with some of the fluids mentioned.

Binaural stethoscopes and phonendoscopes were used, of the type commonly employed in clinical work. The receptors were of several forms: bells, cones, diaphragms, small funnels, or glass cylinders.

Some observations were made by applying a crystal microphone to the fragment of thoracic or abdominal wall, and leading the electrical waves thus produced through an amplifier into a cathode-ray oscillograph and a loud-speaker. The sounds could then be seen on the face of the cathode-ray oscillograph tube or heard from the loud-speaker by several observers. Since the electrical records

of complex auditory phenomena do not furnish any information as to the acoustic characteristics of the sounds, and since measurement of the intensity of the sounds recorded is an elaborate process and can only be performed in an indirect manner, no graphic records are presented of the observations made in this way. Such observations, however, fully confirmed those obtained directly.

The sounds heard under the conditions to be reported were frequently listened to by independent observers. No discrepancies of opinion occurred.

Many different preparations may be made with the thoracic or abdominal walls. A few of the most commonly used will be mentioned.

1. Removal of the thoracic skin; opening of the thoracic cavity in the midline; separation of the mediastinum to one side or total extirpation of it; wide opening of the thoracic cavity by means of hooks or clamps attached to the animal board; application of the receptor of the stethoscope on the outside surface of one hemithorax, fixing it by means of an adequate clamp; cleaning of the parietal pleura with normal saline to remove the blood, hairs, etc., which may have been deposited during the previous maneuvers and might not be recognized macroscopically; friction of the pleura with the isolated heart, spleen, or one of the small lobes of the liver at the region underlying the receptor. These organs were extracted and preserved with all the precautions necessary to avoid damage to their endothelial lining and to eliminate foreign bodies.

2. Removal of the thoracic skin; section of the ribs on both sides of the spinal column, thus obtaining a fragment which comprises the costal and sternal regions (the section at the neck and abdomen need not be described); fixation of the sternocostal fragment over a stethoscopic receiver by means of clamps and stands.

When producing friction in this preparation, the midline should be avoided because of the remnants of the retrosternal section of the mediastinum (mesopericardiac ligament, Ranvier¹⁴). Two types of experiment may be performed with this preparation: (1) A receiver is placed on one of the hemithoraces distal from the sternum. Friction is exerted on the inside over the ribs and intercostal spaces. (2) The receiver is fixed similarly. The fragment is then bent, using the chondrosternal joint on the same side as a hinge, so that these joints become prominent. Then a firm organ is rubbed against these joints. A bent hepatic lobe or fragment of left ventricular wall may be used. The possibility of bleeding or oozing should be kept in mind, and, if necessary, the preparation should be washed with normal saline. Here again, the attachment of the mediastinum should be avoided.

3. Removal of the thoracic skin; separation of a hemithorax by section of the ribs at the spinal column and near the sternum; holding this fanlike fragment with two large clamps placed in a direction parallel to the ribs at the ends; fixation of the preparation on stands so that by tension exerted on the handles of the clamps by means of rubber bands it is possible to distend the intercostal spaces at will. The placing of the stethoscope and the friction are performed as in the previous cases.

4. Removal of the abdominal skin; extirpation of the abdominal wall by cutting along the pelvic, thoracic, and vertebral insertions. This rhomboidal fragment can be utilized as a whole or in part. On one side it is fixed firmly by means of a large clamp, and to the other side a clip is attached on which variable weights may be applied. The receiver is placed underneath the tense horizontal membrane. The peritoneum is rubbed as in the previous examples, or else by means of any solid body covered with another abdominal fragment.

5. A piece of abdominal wall is tied to the base of a glass cylinder 5 cm. in diameter. Variable pressures may be exerted by means of a manometer. The receiver of the stethoscope is similarly covered by abdominal wall with its peritoneum. When the friction is made, it will occur only on a very small area,

because of the convexity of the tissues on the glass cylinder. The small size of the area of contact is further controlled by looking at the preparation tangentially against a light. Movements of the receiver can be made by hand or by means of silent movable stands.

These five preparations may be combined in countless ways. The abdominal viscera, especially, may be used in a wide variety of ways.

The physiologic state of the serosae and lubricating fluids can be readily changed so as to reproduce the clinical phenomena. The effect of drying, roughening, and interposition of clots of blood or lycopodium powder can be studied under fully controlled conditions.

In another series of observations the two following preparations were used:

6. Opening of the left ventricle of a large dog; fixation of the receiver in different parts of the surface of the ventricle; friction between the endocardium and different test objects (chordae tendineae, cusps, etc.) in several places.

7. Removal of the heart of a large dog after previous ligation of the vessels; further distention of the right auricle and ventricle by injection of water through one of the cavae; application of the stethoscope to the apex; and friction at different points, mainly at the posterior wall of the right auricle.

RESULTS

It appears unnecessary to report in detail the observations made under the several experimental conditions described. The following general statements summarize the results with all the preparations tested.

1. In all the normal serosae, noises and sounds will be caused by sliding when they are really in contact. If the lubricating fluids prevent their contact, no sound may be heard.

2. The tension of the subendothelial membranes and the hardness of the organs covered by the serosae are the two factors indispensable for the force of attrition to make the contact possible.

3. Normal serosae adequately lubricated (by normal saline, Ringer's solution, oxalated blood, blood plasma, blood serum) yield noises and sounds which depend on the elasticity of the structures covered by the serosae.

4. These elastic vibrations appear as noises of countless qualities and sounds of diverse loudnesses, pitches, and qualities.

5. All kinds of murmurs may be reproduced by the friction of structures covered with normal endothelium: soft, blowing, scraping, squeaking, musical, etc. All the intermediate varieties of dry murmur and typical friction rub can also be obtained.

6. All kinds of murmurs and friction rubs may also be obtained by the attrition of structures in which the endothelial lining is abnormal or absent.

7. The typical friction rubs are produced more readily by separating the structures in contact than by sliding.

8. Friction rubs may be reproduced by interposition of foreign bodies between normal serosae, e.g., clots of blood, lycopodium powder, etc.

9. All the noises mentioned may be transmitted for long distances. Friction at the posterior wall of the right auricle is clearly heard at the

apex (observation 7) even when the movement of the surfaces in contact is only a few millimeters.

10. A typical friction rub may be transmitted with the acoustic characteristics of a blowing murmur.

11. Acoustic manifestations are greater when the friction is exerted along an axis perpendicular to the direction of the muscular, tendinous, and elastic fibers or of the subendothelial irregularities, other conditions being equal.

No acoustic or tactile vibrations are produced by the sliding of structures covered with endothelium when the sliding is indirect, i.e., when the surfaces are separated by a lubricating fluid and the pressure is slight.

DISCUSSION

Before analyzing the practical importance of the data reported, it is pertinent to review briefly some of the physical principles related to the subject.

As is well known, acoustics is a chapter in the theory of elasticity (see any standard textbook of physics).

Four types of solid bodies are specially considered in acoustics: strings, rods, membranes, and plates. Sound is the result of rapid oscillations of elastic bodies. These vibrations are produced by plucking, percussion, or friction.

Transversal vibrations of strings are produced by friction, as in the violin; by striking, as in the piano; by plucking, as in the harp. The characteristics of these vibrations depend on the length, the thickness, the tension, and the density of the string. Longitudinal vibrations yield higher-pitched sounds than those produced by transversal vibrations. The tension of the string has no influence on the frequency of the longitudinal vibrations.

Vibrations of membranes are produced by the same factors which influence strings. The sound obtained is higher-pitched when the area decreases or the tension increases, under equal conditions of thickness and density. In uniform plane membranes with constant density, the frequencies of the fundamental tones vary with the shape, even though the area remains unchanged.

Friction is caused by the minute irregularities of the surfaces of solid bodies. These irregularities are always present, even on the smoothest surface. The possibility of obtaining friction implies a certain compressibility of the solids employed. Whether the surface asperities will be crushed, broken, or elastically deformed during friction depends on the nature of the bodies concerned. "The force of friction" is the force tangential to the contact surfaces which opposes the relative movement of the solids studied. Surfaces of the same nature offer a greater resistance to friction than those of different nature, because the size and pattern of their irregularities are similar and a better fit is therefore obtained.

Static friction, or friction of adherence, is that which occurs between adjacent quiet bodies. Kinetic friction is that which occurs during movement. Indirect friction is that which appears between lubricated bodies. The variable resistance to movement, or coefficient of friction, is not a constant quantity, but a value which depends on several factors. The laws of Coulomb, Hirn, and Petroff may be summarized as follows as regards their applicability to the present problem:

(1) The coefficient of friction is proportional to pressure; (2) it depends on the nature of the bodies and the state of their surfaces; (3) it is independent of the area of the surfaces of contact, other conditions being equal; (4) when a movement is started it is independent of the speed; (5) when the compressible bodies have been in contact for some time, the coefficient is greater when the movement is started than during the movement (this difference is negligible for hard bodies); (6) the coefficient is inversely proportional to the depth of the coat of lubricating fluids in indirect frictions.

It may finally be mentioned that the elastic vibrations originated by sliding or friction may be appreciated acoustically or by touch.

The experimental data reported in the present study may be divided into two categories: (1) Noises produced by direct friction of normal serosae; (2) noises originated by direct friction of abnormal serosae. There is no fundamental difference between normal and abnormal serosae from the standpoint of the acoustic phenomena engendered by friction. The sounds obtained in either case are indistinguishable. They appear in identical conditions. The only factors of importance in the production of the elastic vibrations which originate the acoustic phenomena are the efficient tension or hardness of the underlying structures and the variable force of friction which brings their elasticity into action.

It is important to emphasize that the sounds observed, even those which occur when the bodies in contact are separated, do not occur in the endothelium but in the subendothelial structures. The efficient cause is the physical property of these structures; the determining cause is the force of friction; and the adjuvant causes are the qualities of the endothelial lining and of the interposed fluid or solid substances. Since the efficient cause is always the same, the uniformity of the acoustic phenomena is readily understood. The multiplicity and mutability of these acoustic manifestations are a consequence of the variations in the subendothelial elasticity and of the indefinite number of combinations between the determining and adjuvant factors. The transmission of these phenomena is but a special aspect of the general subject of propagation of sound and need not be considered here.

Is it possible that normal individuals generate noises due to the physiologic sliding of serosae?

This possibility cannot be denied *a priori*, because, physiologically, pressures exist which are capable of engendering direct frictions.* In the experimental study quite intense sounds appeared when the pressure between the normal membranes was no greater than 2 cm. of mercury. It may therefore be concluded that the pressures which exist in some of the mediastinal organs are sufficient to produce direct friction between structures which anatomically and functionally fulfill the experimental conditions.

Do such acoustic phenomena, similar to the sounds produced experimentally, actually occur in the normal individual? If they do, can they be explained by the friction of serosae? It is well known that such acoustic phenomena are audible in healthy individuals. These physiologic sounds vary considerably. Although some of them cannot be described precisely, they may be classified into two general groups: murmurs and friction rubs. Functional (physiologic), transitory, and inorganic murmurs over the precordial region are very frequent. The physiologists and clinicians are familiar with them. Proteiform noises which do not have the characteristics of murmurs are not so well known.^{5, 8, 15, 16}

Other similar observations cannot properly be judged as applicable to normal individuals.^{4, 7, 9, 11, 12, 17-50}

The next question to be answered is whether these physiologic sounds and those which appear in normal endothelia, in subjects who are not otherwise normal, can be accounted for by the observations reported here. It is generally admitted that these acoustic phenomena are due to the elastic vibrations of structures in the mediastinum. Since direct friction is a known cause of vibration, it is reasonable to attribute them to interserous friction when the conditions pointed out are fulfilled.

It may be stressed again that the friction of normal endothelium produces experimentally all the acoustic manifestations mentioned and that the sliding of abnormal endothelium of serosae likewise sets up audible vibrations. The conditions in which both these sets of acoustic phenomena can be reproduced throw light upon two very important problems of cardiology and physical diagnosis of the thorax: (a) contradictions between the clinical picture and the post-mortem findings; (b) contradictions between the physical signs and the functional disturbances. These surprising and numerous contradictions clearly denote the inability of the classical theories to cope with all the problems of auscultation. The data presented complement these classical theories and account for these hitherto puzzling problems. The form, location, and size of the organs, and also the tension and friction forces which occur at the heart, the pericardium, and the pleurae in the normal subject and in cases of thoracic disease afford a logical basis for fruitful analysis

*Direct friction occurs when there is a lubricating fluid, if the force applied is sufficient to displace it.

of all the obscure problems of auscultatory semeiology. The fact that not all normal hearts present murmurs and friction rubs does not invalidate the preceding conclusions. In the first place, the conditions for the appearance of these sounds are several; if one of them should be lacking, the sounds would not occur. Furthermore, the heart sounds will interfere in circumstances so obvious that it is not necessary to mention them; they may mask, change, or re-enforce the acoustic manifestations due to friction. A similar argument applies to the cases in which obvious lesions in the serosae of the heart and surrounding structures do not lead to the appearance of the expected rubbing sounds.

A few clinical instances selected at random will now be analyzed in the light of the present study, for illustrative purposes.

1. *Pericardial Processes (pericarditis, infarcts, "milk spots")*.—The murmurs of evident pericarditis, with no demonstrable manifestations in the cardiac muscle or valvular systems, their topographical and chronological instability, their changes into friction rubs, can all be explained on the basis of the murmurs of serous origin. This statement does not imply a negation of the possibility of adventitious noises appearing according to the classical theory of fluid eddy currents, when it is possible to prove clinically that the necessary conditions are present. The statement of Soulier,¹³ although contradicted by Potain, is correct, that murmurs may appear in pericarditis when the endothelium is altered, and that murmurs may also appear when this alteration is not of inflammatory origin. The murmurs which precede the rubs caused by myocardial infarction and those which persist⁵¹ during its evolution, with the characteristics described by Castex,⁵² can also be due to the serous frictions. A post-mortem examination of pieces of infarct and repetition of the experiments 6 and 7, described previously, will necessarily suggest that some of the pericardial sounds are similar to those reproduced in the laboratory. The thesis that "milk spots"^{56, 53} are a source of adventitious sounds, although the surface is smooth, is supported by the present evidence. It is likely that other equally slight pericardial alterations will produce similar effects.⁵⁴⁻⁶⁷

2. *The Endocardial Processes (without demonstrable valve lesions or anomalies in the capacity of the cavities)*.—The region of the heart where most intense friction may occur is obviously the left ventricle, and roughening of the lining is frequent in this region. The possibility that sounds may be set up by frictions in this cavity cannot be denied even when the pathologic changes are minimal.^{6, 68-80} Especially during the silence of diastole, the clinician may interpret many adventitious sounds as due to serous frictions. The structure of the mitral valve, its fineness,⁸¹ its tension during systole, the localization and histologic situation of the tiny vegetations in some varieties and periods of endocarditis suggest the possibility that certain mero-systolic and holosystolic murmurs may be due to vibrations from serous frictions, similar to those produced

by liquid currents. If it is accepted that murmurs of liquid-current origin are produced by transversal vibrations,^{53, 69, 82, 83} then the conclusion cannot be avoided that such vibrations may be set up by friction (the vibrating structures are practically a conglomerate of tense strings), regardless of what physiologic theory is adopted to explain the closure of the orifice. What was stated previously for accidental and inorganic murmurs may apply to the present phenomena. Why should the clinician insist on limiting his hypothesis to the theory of eddy currents in the cases in which the roentgenograms demonstrate a normal heart and there are no signs of any hydraulic disturbance?

3. *The Extracardiac Processes.*—The methodical critique which Tripier and Devic¹⁶ have made of the theory suggested by Laënnec¹ and later developed by Potain,⁸⁴ on the role of the lung borders overlapping the heart, has not been adequately answered. The data summarized by Fahr⁸⁵ also cast doubt on Laënnec's theory. The interpretation adopted here for murmurs of serous origin may extend to all acoustic phenomena in the mediastinum when the lesions which the classical theories require cannot be demonstrated satisfactorily.⁸⁶⁻¹¹²

SUMMARY

The acoustic phenomena produced by friction of organs covered by normal and abnormal serosae, lubricated by normal and abnormal fluids, were studied in rabbits, cats, and dogs.

Direct friction of structures covered by normal endothelium, lubricated by normal, physiologic fluids, is a source of murmurs and friction rubs.

Direct friction of structures covered by abnormal serosae is also a source of murmurs and friction rubs.

The importance of these data for the correlation of clinical, pathologic, and post-mortem findings is discussed.

REFERENCES

1. Laënnec, R. T. H.: *Traité de l'Auscultation Médiate et des Maladies des Poumons et du Cœur*, Paris, 1831.
2. Mackenzie, Sir J.: *Diseases of the Heart*, 1925.
3. Aran, F. A.: *A Practical Manual of the Diseases of the Heart and Great Vessels*, Philadelphia, 1843.
4. Buttler, G. A.: *The Diagnostics of Internal Medicine*, p. 381, New York, 1906.
5. Colbeck, E. H.: *Diseases of the Heart*, London, 1901, Methuen and Co.
6. Gerhardt, C.: *Lehrbuch der Auscultation und Perkussion*, Tübingen, 1871.
7. Gibson, G. A.: *The Action of the Auricles in Health and Disease*, Edinburgh M. J. 28: 119, 1882.
8. Hare, H. A.: *An Undescribed Cardiac Sound*, Tr. A. Am. Physicians 16: 1, 1901.
9. Money, A.: *On the Great Frequency of Cardiac Murmurs in the Puerperal State*, Med. Chir. Tr. London 65: 87, 1882.
10. Seitz, J.: *Zur Lehre von der Ueberanstrengung des Herzens*, Deutsches Arch. f. klin. Med. 12: 297, 602, 1874.
11. Smith, A. H.: *Valvular Friction Sounds*, J. A. M. A. 4: 576, 1885.
12. Solis-Cohen, M.: *A Xiphosternal Crunching Sound*, Am. J. M. Sc. 126: 131, 1903.
13. Soulier, H.: *Le Frottement Rythmique de Deux Surfaces peut Engendrer un Souffle; Frottement Péricardique et Souffles Cardiaques Anorganiques*, Lyon Méd. 90: 611, 1899.

14. Ranvier, L.: *Traité Technique d'Histologie*, Paris, 1889.
15. Géndrin, A. N.: *Leçons sur les Maladies du Cœur, et des Grosses Artères*, Paris, 1841.
16. Tripier and Devic: *Traité de Pathologie Générale* du Bouchard, Paris, 1897.
17. Bramwell, C., and Ellis, R.: The Crescendo Murmur of Mitral Stenosis, *J. Physiol.* 67: 1929.
18. Bramwell, C., and Ellis, R.: Some Observations on the Circulatory Mechanism in Marathon Runners, 1929, *Quart. J. Med.* 24: 329, 1930.
19. Bridgman, E. W.: Notes on a Normal Presystolic Sound, *Arch. Int. Med.* 14: 475, 1914.
20. Brown, F. J.: Xiphisternal or Pericardial Chisel-Sound, With Its Practical Application, *A. M. J. London* 384: 409, 1856.
21. Cabot, R. C.: *Physical Diagnosis*, New York, 1915.
22. Cabot, R. C.: *Facts on the Heart*, Philadelphia-London, 1926, W. B. Saunders Co.
23. Da Costa, J. M.: On Functional Valvular Disorders of the Heart, *Am. J. M. Sc.* 58: 1869.
24. Epstein, J.: Myatonic Cardiac Murmurs, *Arch. Pediat.* 48: 635, 1931.
25. Flint, A.: The Mitral Cardiac Murmurs, *Am. J. M. Sc.* 91: 27, 1886.
26. Friedlander, R. C., Brown, M. G.: Systolic Murmur: Further Observations on Its Clinical Significance, *Ann. Int. Med.* 8: 893, 1935.
27. Freeman, A. R., Levine, S. A.: The Clinical Significance of the Systolic Murmur, *Ann. Int. Med.* 6: 1371, 1933.
28. Gibbs, J. H.: Heart Murmurs: Their Incidence and Interpretation, *AM. HEART J.* 4: 305, 1929.
29. Goodall, J. S.: The Heart in Graves' Disease, *Practitioner* 105: 37, 1920.
30. Howell, F.: Physiological Heart Murmurs Produced by Electric Light Baths, *Boston M. Surg. J.* 357, 1902.
31. Irons, E. E., Jennings, A.: Presystolic Murmurs in Rapid Hearts Simulating Murmur of Mitral Stenosis. With Report of Necropsies, *J. A. M. A.* 78: 957, 1922.
32. Jacobi: Functionelle und organische Herzgeräusche im Kindesalter, *Klin. Therap. Wehnschr.* 22: 674, 1900.
33. King, J. T.: Auscultatory Phenomena of the Heart in Normal Men and in Soldiers With Irritable Heart, *Arch. Int. Med.* 24: 89, 1919.
34. Lee, R. I.: The Physical Examination of Apparently Healthy Individuals; Its Importance, Limitations and Opportunities, *Boston M. Surg. J.* 188: 929, 1923.
35. Lewis, Th. J.: The Disappearance of Abnormal Heart Sounds, *Brit. M. J.* 1: 328, 1918.
36. Mayet, F. O.: *Traité de Diagnostie Médical et de Séméiologie*, Paris, 1899.
37. Morse, L. J.: Functional Diastolic Murmurs in Aortic Area and Pistol Shot Sounds in Groins in Infancy and Childhood, *J. A. M. A.* 83: 300, 1924.
38. Morris, R. S., Friedlander, A.: The Significance of Presystolic Thrills in the Examination of Soldiers, *J. A. M. A.* 71: 375, 1918.
39. Neuhof, S.: The Irritable Heart in General Practice. A Comparison Between It and the Irritable Heart of Soldiers, *Arch. Int. Med.* 1: 50, 1919.
40. Parmenter, D.: Occurrence and Significance of Systolic Murmurs in Healthy Individuals, *J. A. M. A.* 78: 1680, 1922.
41. Phear, A. G.: On Presystolic Apex Murmur Without Mitral Stenosis. (Read as a Thesis at the University of Cambridge on May 29, 1895.) *Lancet* 2: 716, 1895.
42. Reid, Wm. D.: The First Heart Sound and the Presystolic Murmur, *J. A. M. A.* 76: 432, 1921.
43. Reid, Wm. D.: Heart Murmurs in the Practice of Medicine, *New England J. Med.* 204: 597, 1931.
44. Roberts, F. T.: A System of Medicine, Allbnt, C., and Ralleston, H. D. 4: 1909.
45. Russel, Wm.: The Murmurs of Debility in the Pulmonary and Tricuspid Areas, *Edinburgh M. J.* 28: 130, 1882.
46. Sansom, E.: *The Diagnosis of Diseases of the Heart and Thoracic Aorta*, Philadelphia, 1892.
47. Sewall, H. S.: A Common Modification of the First Sound of the Normal Heart Simulating That Heard With Mitral Stenosis, *Tr. A. Am. Physicians* 24: 459, 1909.
48. Siemsen, W. J.: Evaluation of Nonorganic Auscultatory Cardiac Findings and the Venous Hum in Children, *Am. J. Dis. Child.* 47: 1100, 1934.

49. Thayer, Wm. S.: Observations on Some of the Commoner Deviations From the Ordinary Met Within the Examination of the Heart of Supposedly Normal Individuals, *Med. Record* 91: 617, 1917.
50. Idem: Reflections on the Interpretation of Systolic Cardiac Murmurs, *Am. J. M. Sc.* 169: 313, 1925.
51. Wolferth, Ch. C., Wood, F. C., and Margolies, A.: An Auriculosystolic Murmur in the "Tricuspid Area" During Convalescence From Acute Coronary Occlusion, *Am. J. M. Sc.* 186: 496, 1933.
52. Castex, M. R.: Los Soplos del Corazón, *Prensa méd. argent.* 19: 1153, 1932.
53. Edens, E.: *Lehrbuch der Perkussion und Auskultation*, Berlin, 1920.
54. Collin, V.: *Manual for the Use of the Stethoscope*, London, 1829.
55. Collin, V.: *Des Diverses Méthodes d'Exploration de la Poitrine, et de leur Application au Diagnostic de ses Maladies*, Paris, 1831.
56. Coombs, C.: The Microscopic or "Submiliary" Nodules of Active Rheumatic Carditis, *J. Path. & Bact.* 15: 489, 1910.
57. Coombs, C.: *Rheumatic Heart Disease*, New York, 1924.
58. Friedberg, Ch. K.: Pericardial Lesions in Rheumatic Fever, *Am. J. Path.* 12: 183, 1936.
59. Futeher, T. B.: A Study of Subcutaneous Fibroid Nodules, *Bull. Johns Hopkins Hosp.* Sept-Oct., p. 133, 1895.
60. Hope, J. A.: *A Treatise on the Diseases of the Heart and Great Vessels*, Philadelphia-London, 1842.
61. Johnson, G.: A Clinical Lecture on Triple Pericardial Sound, and on Reduplication of the First Sound of the Heart, *Lancet*, p. 697, May, 1876.
62. Matrai: Ueber pericardiales Sehnenpfeifen, *Wien. Med. Blätter.* 8: 1887.
63. McGlenahan, W., and Paul, J. R.: A Review of the Pleural and Pulmonary Lesions in Twenty-Eight Fatal Cases of Active Rheumatic Fever, *Arch. Path.* 8: 595, 1929.
64. Pilod-Passa: A propos de l'Intérêt Diagnostique du Frottement Péricardique Rhumatismal, *Press méd.* 42: 1296, 1934.
65. Poirier, P.: L'Appareil Séro-Grasieux du Coeur, *Presse méd.*, p. 777, 1904.
66. Robinson, R.: *Anatomie et Pathologie des Séro-Appendices*, Paris, 1908.
67. Waldorp, C., and Genijovich, S.: Enfermedades del Pericardio, Buenos Aires, 1933.
68. Cohn, A. E.: The Formation of Endothelial Pockets in Aortic Insufficiency, *New York Path. Soc.* 14: 24, 27, 1914.
69. Geigel, R.: Die Entstehung der Geräusche in Herz und Gefäßen, *Virchows Arch. f. path. Anat.* 140: 385, 1895.
70. Gross, L., and Erlich, J. C.: Studies on the Myocardial Aschoff Body. II. Life Cycle, Sites of Predilection and Relation to Clinical Course of Rheumatic Fever, *Am. J. Path.* 10: 489, 1934.
71. Gross, L., Kugel, M. A., and Epstein, E. Z.: Lesions of the Coronary Arteries and Their Branches in Rheumatic Fever, *Am. J. Path.* 2: 253, 1935.
72. Gross, L.: Lesions in the Roots of the Pulmonary Artery and Aorta in Rheumatic Fever, *Am. J. Path.* 2: 631, 1935; Lesions of the Left Auricle in Rheumatic Fever, *Ibid.* 2: 711, 1935.
73. Gross, L., and Friedberg, Ch. K.: Lesions of the Cardiac Valve Rings in Rheumatic Fever, *Ibid.* 12: 469, 1936.
74. Guitéras, J.: Direct Functional Murmurs and Obstructive Safety-Valve Action in the Heart. *Trans. A. Am. Physicians* 2: 37, 1887.
75. Herzheimer, G.: Ueber Perikardknötchen u. Sehnenflecke, *Virchows Arch. f. path. Anat.* 165: 248, 1901.
76. Jalesky, Th. C.: Myxoma of the Heart Valves, *Am. J. Path.* 10: 399, 1934.
77. Krasso, H.: Ueber atypische endocardiale Taschenbildungen bei Aorteninsuffizienz, *Frankf. Ztschr. f. Path.* 32: 173, 1925.
78. Ribbert: Beiträge zur pathologischen Anatomie des Herzens, *Virchows Arch. f. path. Anat.* 147: 193, 1897.
79. Vaquez, H.: *Maladies du Coeur*, Paris, 1921, J. B. Baillière et fils.
80. Zahn, E. W.: Ueber einige anatomische Kennzeichen der Herzklappen-Insuffizienzen, *Verhandl. d. Kong. f. innere Med.* 13: 351, 1895.
81. Bethe, A., Bergmann, G., Embden, G., and Ellinger, A.: *Handbuch der Normalen und Pathologischen Physiologie*, Vol. 2, Berlin, 1926, Julius Springer.
82. Wiggers, C. J.: *Modern Aspects of the Circulation in Health and Disease*, Philadelphia, 1923.
83. *Ibid.*: *Physiology in Health and in Disease*, Philadelphia, 1934.
84. Potain, B. C. E.: Des Bruits Extracardiaques, *Semaine méd.*, p. 20, 1885.

85. Fahr, G.: The Acoustics of the Bronchial Breath Sounds, *Arch. Int. Med.* 39: 286, 1927.
86. Barié, E.: *Bruits de Souffle et Bruits de Galop*, Paris, 1894.
87. Barié, E.: *Traité Pratique des Maladies du Coeur et de l'Aorte*, Paris, 1912.
88. Bendove, R. A.: Roentgenology as an Investigational Field in the Mechanism and Diagnosis Significance of Physical Signs of the Chest, *Am. J. M. Sc.* 173: 322, 1927.
89. Beuter, C.: *Des Souffles Diastoliques de la Base du Coeur (Souffles Anorganiques Surtout)*. Th. Lyon, 1906.
90. Bland, E. F., White, P. D., and Jones, T. D.: The Development of Mitral Stenosis in Young People, *AM. HEART J.* 10: 995, 1935.
91. Bland, E. F., Jones, T. D., and White, P. D.: Disappearance of the Physical Signs of Rheumatic Heart Disease, *J. A. M. A.* 107: 569, 1936.
92. Bouillaud, J.: *Traité Clinique des Maladies du Coeur*, Paris, 1841.
93. Bramwell, C.: Sounds and Murmurs Produced by Auricular Systole, *Quart. J. Med. New Series* 4: 139, 1935.
94. Broadbent, J. F. H.: *Adherent Pericardium*, New York, 1896.
95. Descheid, G., and Toussaint, P.: Les Inflammations Pleurales, *Presse méd.* 53: 1060, 1935.
96. Duponchel, P.: Des Souffles Cardiaques d'Origine Adhérentielle, *Gaz. d. hôp.* 104: 1155, 1900.
97. Fiorito, E. S.: Vesiculas Subpleurales, *Act. Trab. V. Congr. N. d. Med. Rosario*, 427, 1934.
98. Floyd, R.: *Studies on the Heart, Arteries and Kidneys*, New York, 1930, Pandick Press, Inc.
99. Génévrier, J., and Descops, H.: Syndrome Artériel Pulmonaire dans la Sinistocardie, *Presse méd.* 53: 1065, 1935.
100. Latham, P. M.: *The Collected Works of Dr. P. M. Latham*, New Sydenham. Soc. London 1: 1876.
101. Lian, C., and Déparis, P.: Le Claquement Mésosystolique Pleuro-Péricardique, *Bull. et mém. Soc. méd. d. hôp. de Paris* 49: 496, 1933.
102. Lian, C., Marchall, M., and Pautrart, J.: Un Signe Clinique de la Calcification du Péricarde: la Vibrance Péricardique Protodiastolique, *Bull. et mém. Soc. méd. d. hôp. de Paris* 49: 20, 1933.
103. See, G.: *Traité des Maladies du Coeur*, Paris, 1889.
104. Skoda, J.: *A Treatise on Auscultation and Percussion*, London, 1854.
105. Sprague, H. B., and White, P. D.: Comparative Study of "Rheumatic" Mitral Regurgitation and Mitral Stenosis, *AM. HEART J.* 1: 629, 1926.
106. Sprague, H. B.: *Auscultation and Heart Sounds*, New England J. Med. 204: 595, 1931.
107. Stokes, Wm.: *Researches on the Diagnosis of Pericarditis*, *Dublin J. M. Chem. Sc.* 4: 29, 1835.
108. Idem: *Diseases of the Heart and Aorta*, Philadelphia, 1854.
109. Thorburn, J.: Pulsatile Respiration, *Brit. M. J.* 2: 305, 1862.
110. White, P. D.: The Clinical Significance of Apical Murmurs, *Am. J. M. Sc.* 174: 731, 1927.
111. Idem: *Heart Disease*, New York, 1934.
112. Wood, J. D., White, P. D.: The Interpretation of Mitral Diastolic and Aortic Systolic Murmurs, *Clin. North America* 7: 729, 1923.

ELECTROCARDIOGRAPHIC RESPONSE TO GRADUALLY INDUCED OXYGEN DEFICIENCY

I. RESPONSE OF NORMAL HEARTS IN VARIOUS AGE GROUPS

S. H. MAY, M.D.

NEW YORK, N. Y.

IT HAS been known for a long time that induced oxygen deficiency produces striking changes in the electrocardiogram of the human heart. In order to determine the significance of these changes, the degree of correlation between progressive deficiency of oxygen and variation in the electrocardiogram in people with normal hearts in various age groups, and in persons with diseased hearts, as well, has been studied. Whereas this publication is concerned mainly with the reaction of normal hearts, subsequent publications will deal with various groups of patients with heart disease.

REVIEW OF LITERATURE

The first experiments with induced anoxemia were made by Greene and Gilbert, in 1919.¹ They studied and described the specific changes in the electrocardiographic curves in anoxemia produced by the re-breathing method. When Rothschild and Kissin,² who concluded from similar experiments that anoxemia is in part responsible for pain in angina pectoris, studied the electrocardiographic changes, they found them more frequently in patients with angina pectoris than in patients without coronary disease.³ In their study, however, only two normal, healthy subjects were tested. Katz, Hamburger, and Schutz⁴ observed and described the effect of generalized anoxemia on the electrocardiogram of normal subjects. They recorded changes similar to those produced in people suffering from anginal pain. Levy, Barach, and Bruenn,⁵ using a special apparatus which kept the oxygen content of the inspired air constantly at 12 per cent, took electrocardiograms of persons with, and without, cardiac disease. In both groups the typical changes in the form of the electrocardiogram were observed also, but in those with normal hearts they were found to be of minor degree.

Elaborate studies regarding breathing mechanism, blood pressure, degree of oxygen diminution in the expired air,¹⁻⁵ as well as circulation time, venous pressure, and blood oxygen saturation⁵ have been made during the stages of anoxemia. The final oxygen concentration in the expired air varied from 13.5 per cent to 6 per cent. Within this range, neither the onset of discomfort nor the degree of electrocardiographic change seemed to follow closely the decrease of oxygen in the expired air at the end of the test. In studying two normal subjects, Rothschild and Kissin found that one developed S-T changes when the oxygen con-

tent of the exhaled air at the end of the test was 8.1 per cent, and that the other did not show any change when it was 6.1 per cent. No striking difference with respect to their ability to tolerate oxygen want was found among the young and older normal subjects and patients with heart disease.

In none of the investigations was the age of the tested subjects given.

METHODS

For inducing gradually increasing anoxemia, a rebreathing method similar to that already used by Greene and Gilbert¹ was employed. The subject was connected to a Leitz basal metabolism machine (Fig. 1) filled with room-air. The carbon dioxide was removed in the usual way by soda lime. The rebreathing curve was recorded, as in measuring the basal metabolic rate, in order to study the respiratory mechanism during the progressive stages of anoxemia. Before, during, and at approximately three minutes after the test, electrocardiographic records were taken. Only the three standard leads were used because the direct lead did not seem to add anything of importance to the results.

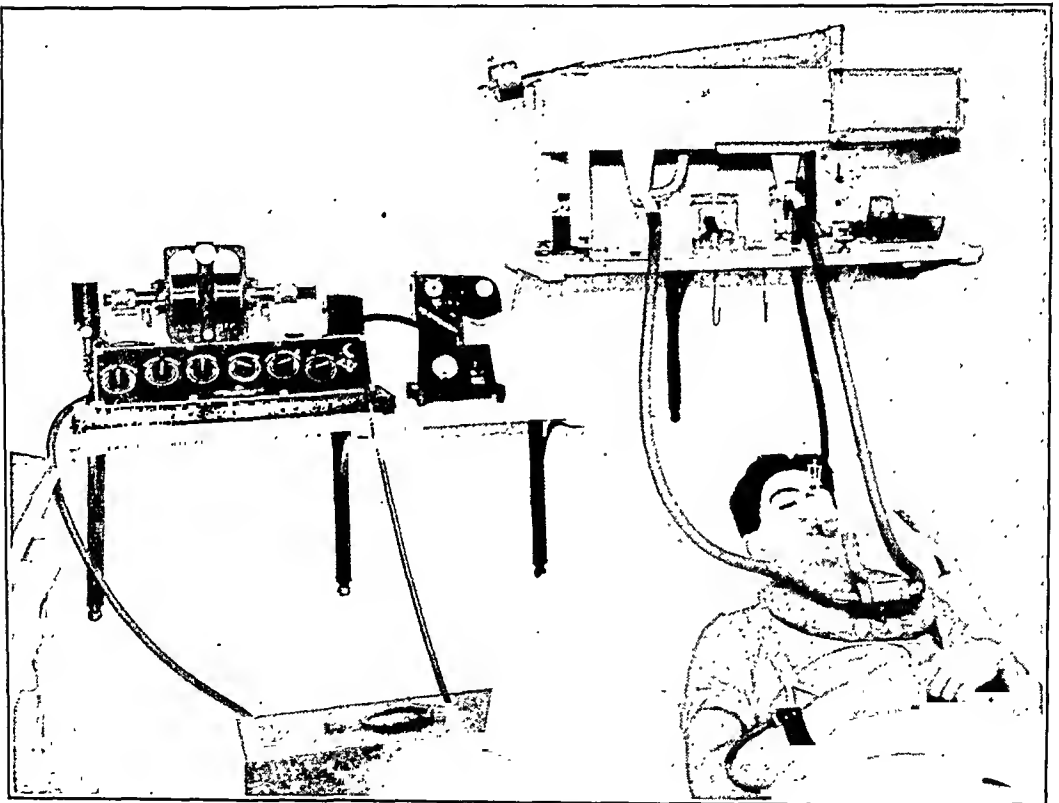


Fig. 1.—Method.

The patient was placed on a comfortable couch, and was told that he might expect some slight discomfort after several minutes of rebreathing, and to raise his arm when the discomfort made him uneasy. He was carefully watched during the test for any signs of cyanosis or dyspnea. When the patient raised his arm, or if dyspnea or cyanosis became severe, the test was stopped. The duration of the test ranged from seven to fourteen minutes and was approximately the same in both normal subjects and patients with heart disease.

Because the time necessary to record an electrocardiogram was from thirty to forty-five seconds, the time given in the legends coincides as nearly as possible with Lead II. Since the last tracing was taken as near the end of the period of anoxemia as possible, Lead III is sometimes disturbed by unrest or by removing the mouth piece and nose clamp.

RESULTS

Fifty individuals whose hearts were thought to be normal, as judged by means of physical, roentgenologic, and electrocardiographic examinations, were tested. When these individuals are arranged according to age, there are found to be ten in the group between fifteen and twenty years, ten in each of the decades from twenty to fifty, and ten between the ages of fifty and seventy. Descriptions of the several age groups, together with illustrative examples in each, follow.

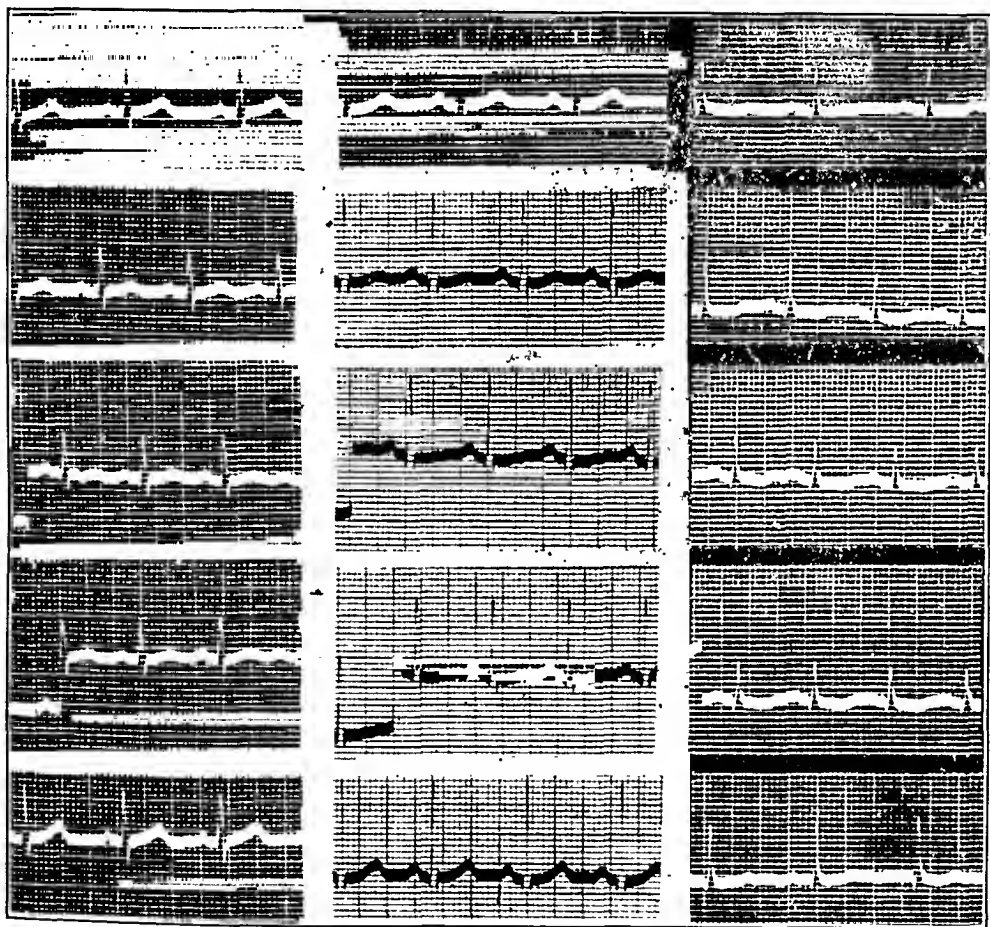


Fig. 2.—F. T. Age, 18. Normal heart. Very athletic. Test: 7 min. Discontinued because of shortness of breath. First record, standard 3 leads. Second, third, and fourth records, 2, 4, and 6½ minutes after beginning to rebreathe. Last record, after 2 minutes of breathing room air.

1. (15 to 20 years.) In this group, four tests showed complete eradication of the T wave (Figs. 2 and 3) in Lead II; four, reduction of the T wave to considerably less than half its original height; and two, a smaller reduction. The subjects whose T waves were eradicated are

very active young people who are athletic and accustomed to competitive sports. The two subjects who showed the most moderate diminution of T_2 are asthenic in type and are unaccustomed to bodily exercise.

2. (20 to 30 years.) This group showed, in general, slightly less change in the electrocardiograms taken during the test than the previous one. There was only one record in which T_2 was abolished (Fig. 4), and there were three in which it was reduced to less than half its original height. The other six records show a very considerable reduction of the height of the T wave (Fig. 5). As before, there was an obvious correlation between the degree of change and the amount of bodily activity.

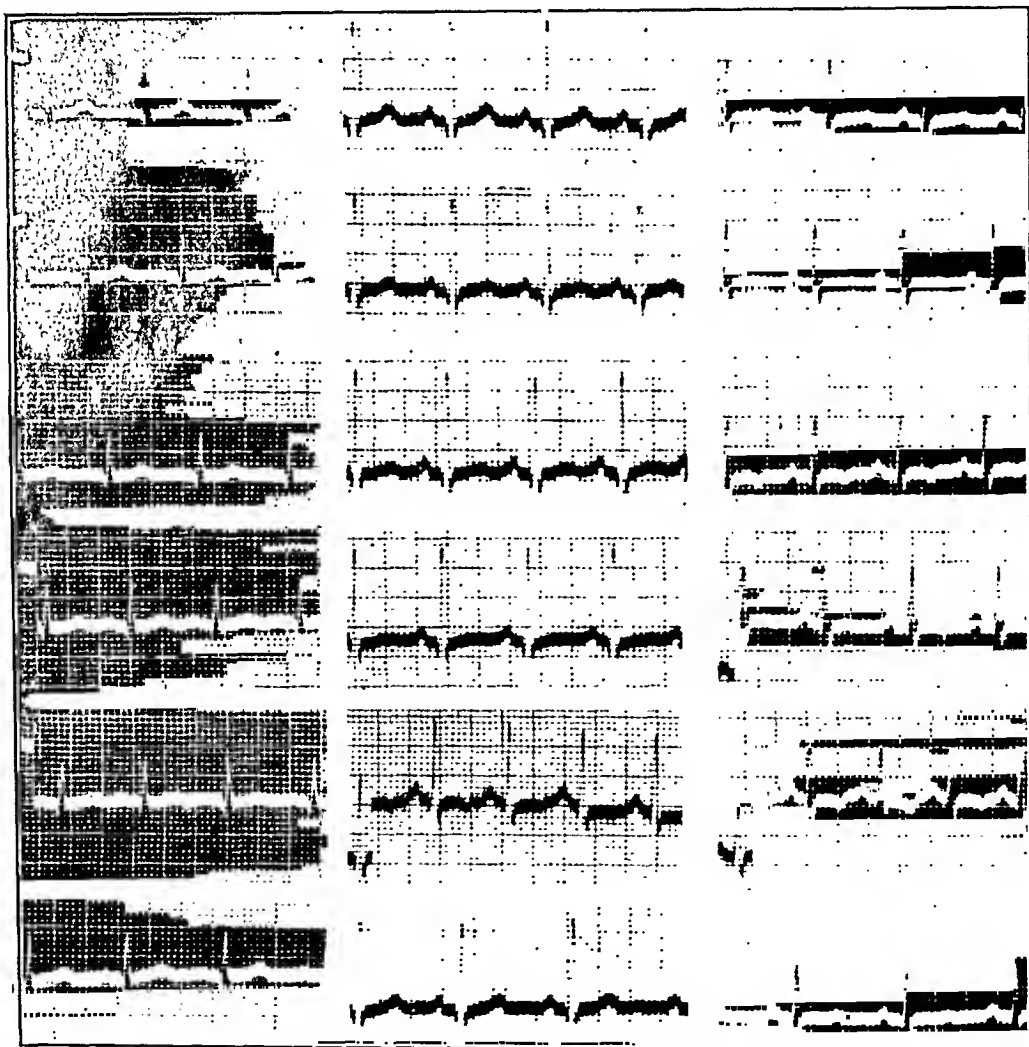


Fig. 3.—E. B. Age, 20. Normal heart. Played football and baseball until 2 years before. Test: 12½ minutes. Discontinued because of marked cyanosis. First record, standard 3 leads. Second, third, fourth, and fifth records, 4, 7, 10½, and 12 min. after beginning to rebreathe. Last record, after 3 min. of breathing room air.

3. (30 to 40 years.) One record of a 31-year-old man with very good exercise tolerance showed complete eradication of T_2 . In four records considerable change in the height of the T wave was seen; in three only moderate diminution was noted; and in two there was almost none.

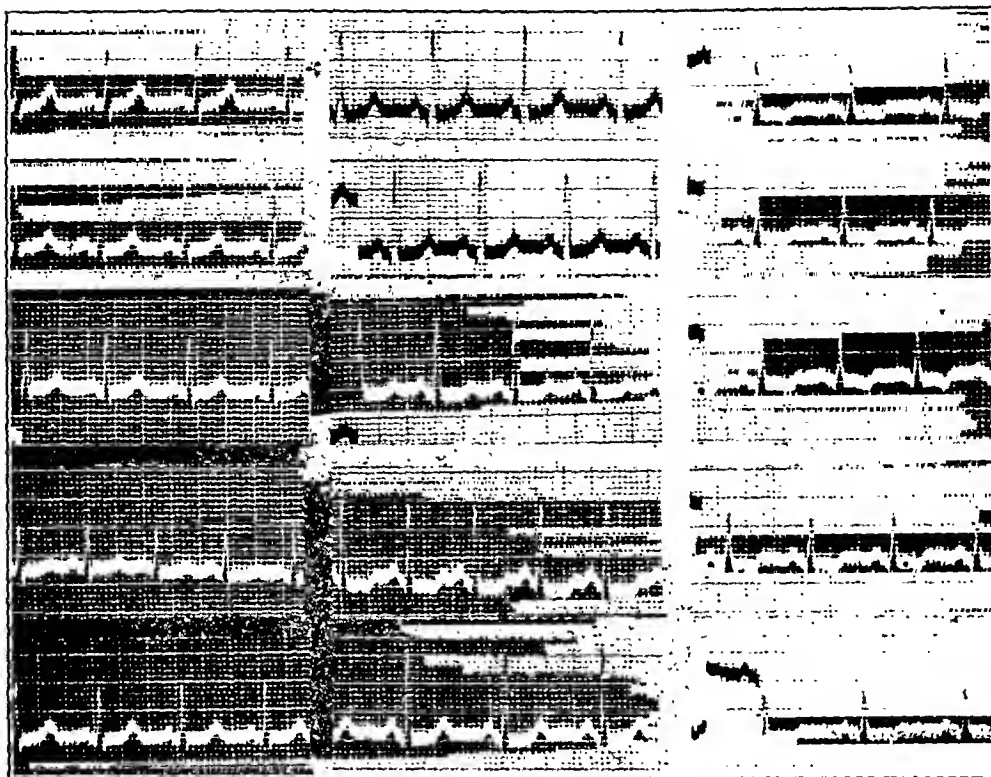


Fig. 4.—A. K. Age, 24. Normal heart. Used to be good long distance swimmer. Test: 8 min. Discontinued because of dyspnea and dizziness. First record, standard 3 leads, second, third, and fourth records 3½, 5½, and 8 min. after beginning to rebreathe. Last record, after 3 min. of breathing room air.

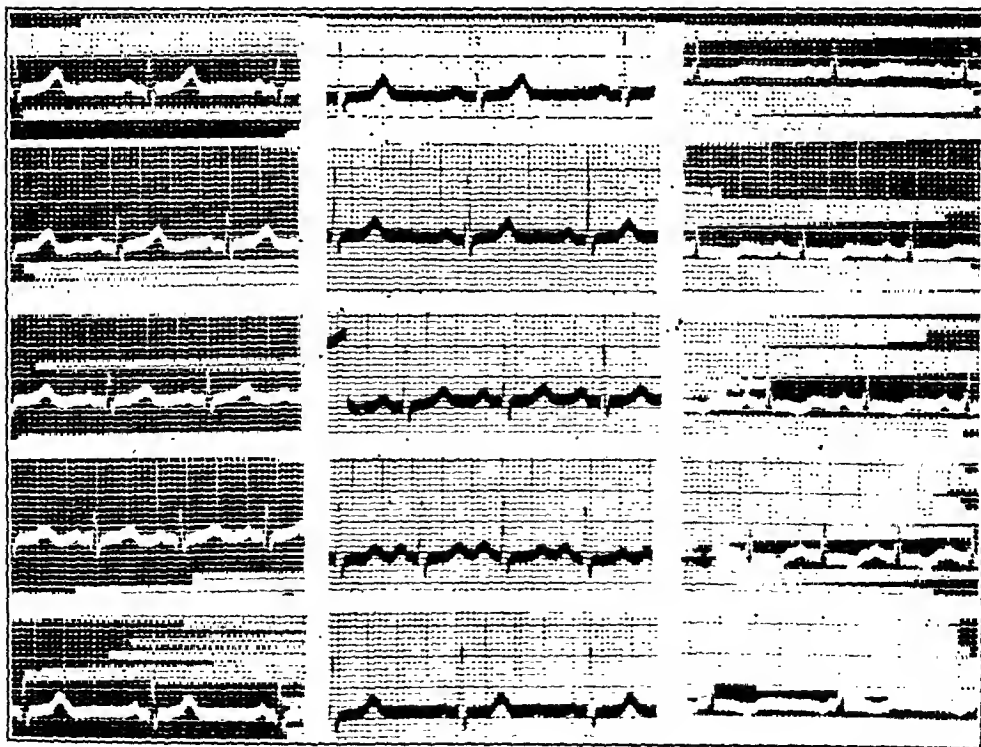


Fig. 5.—J. M. Age, 25. Normal heart. Test: 11 min. Discontinued because of feeling of weakness and shortness of breath. First record, standard 3 leads. Second, third, and fourth records, 3, 6, and 10 min. after beginning to rebreathe. Last record, after 3 min. of breathing room air.

An example of the average diminution of the T wave in Lead II in this group is seen in Fig. 6, in which T decreases to approximately half its original height. Correlation between T-wave diminution and exercise tolerance was very distinct. One of the subjects, in whose records no change occurred, was of the asthenic type, and the other was a young woman who has suffered from purulent otitis media since childhood.

4. (40 to 50 years.) Changes in the T wave became abruptly less pronounced in this group. Decrease of T_2 to less than half its original height was not encountered, and in three records there was no change at all. The average record showed a diminution of about one-fourth of the original height of the T wave (Fig. 7).

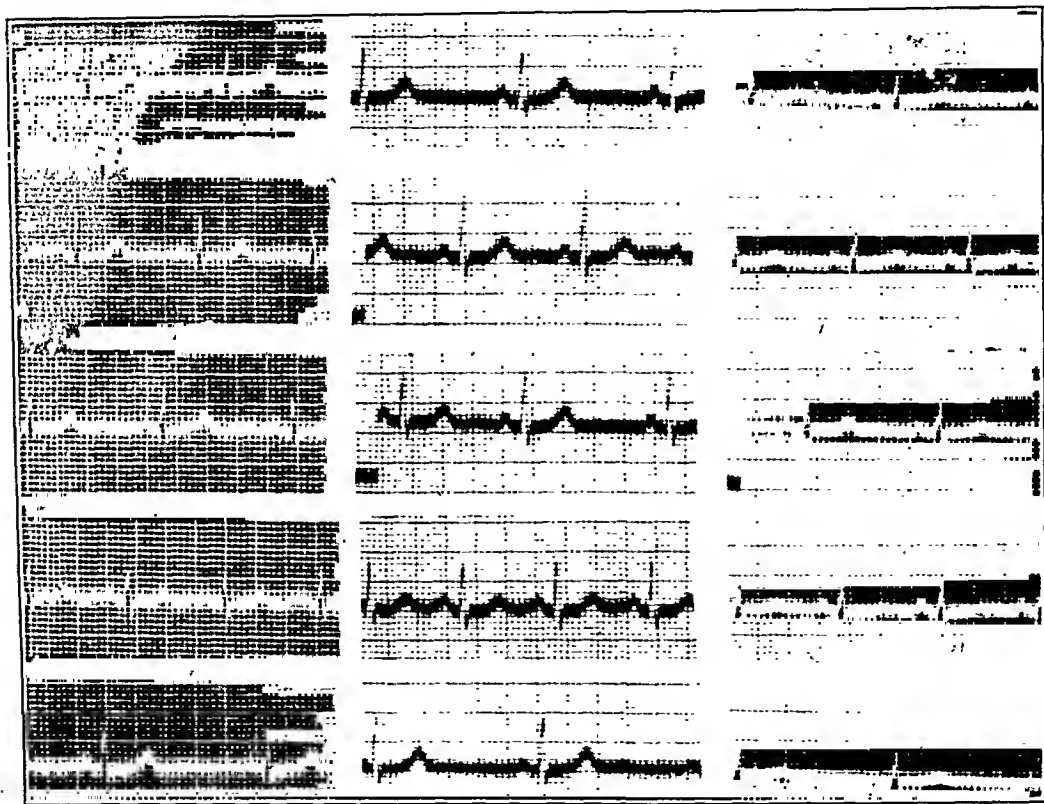


Fig. 6.—E. J. Age, 35. Governess. Normal heart. Test: $14\frac{1}{2}$ min. Discontinued because of dyspnea and cyanosis. First record, standard 3 leads. Second, third, and fourth records, $3\frac{1}{2}$, $7\frac{1}{2}$, and 14 min. after beginning to rebreathe. Last record, after 3 min. of breathing room air.

5. (50 to 70 years.) A further waning of change was noted in the older age group. Only two records showed a diminution of as much as one-third the original height of the T wave. One of these records was obtained from a man who has had long military training, has lived in the tropics for ten years, and appears and acts like a much younger man (Fig. 8). The other man is an assiduous golfer. Five records showed very slight diminution, and three none at all.

Table I summarizes the specific results of the tests in the age groups studied. Emphasis has been put upon changes in Lead II because they were more readily visible and measurable. Corresponding changes,

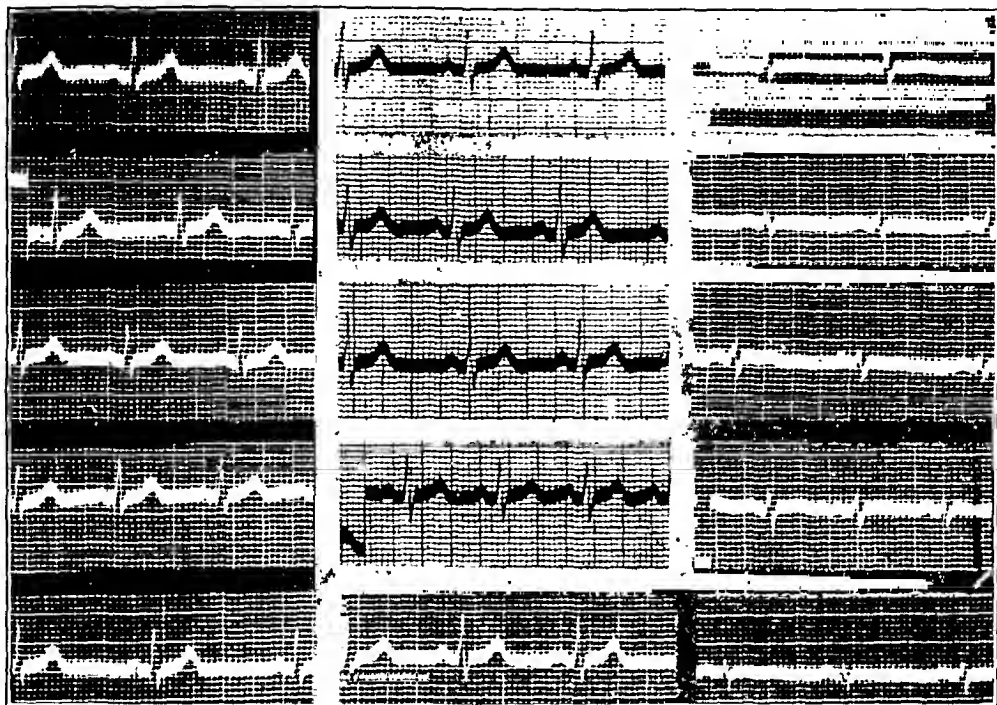


Fig. 7.—E. L. Age, 44. Normal heart. Test: 13 min. Discontinued because of shortness of breath and slight dizziness. First record, standard 3 leads. Second, third, and fourth records, after 4, 7, and 12 min. after beginning to rebreathe. Last record, after 3 min. of breathing room air.

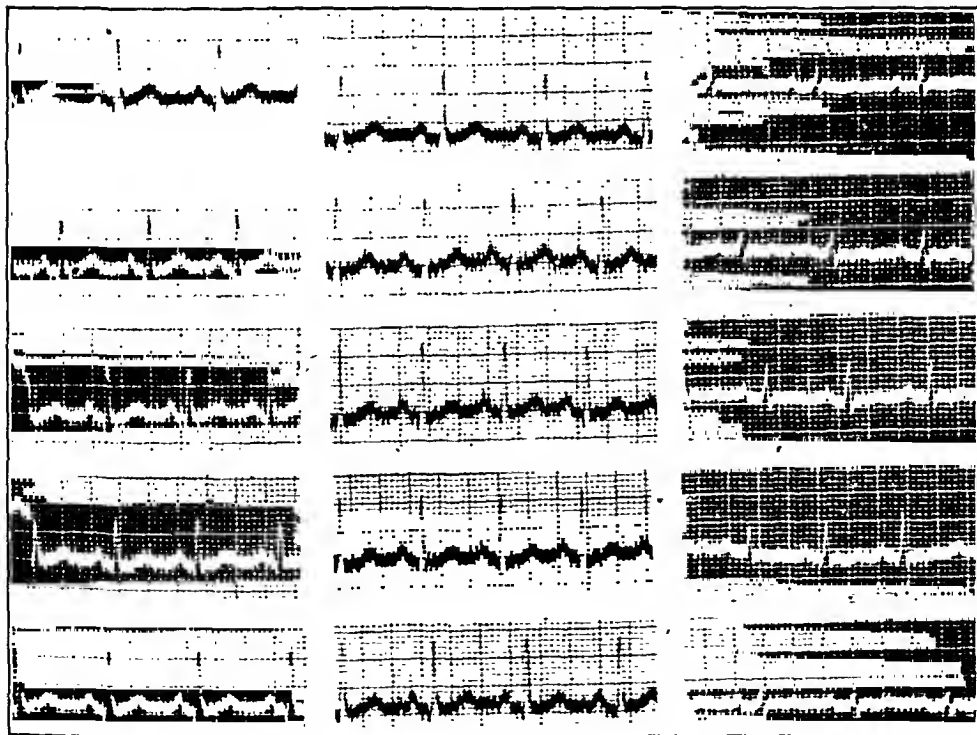


Fig. 8.—M. R. Age, 63. Normal heart. Test: 12 min. Discontinued because of heat in the head and flushes. First record, standard 3 leads. Second, third and fourth records, 4, 7½, and 11 min. after beginning to rebreathe. Last record, after 3 min. of breathing room air.

TABLE I

NAME	AGE	EXERCISE	LENGTH OF TEST (MIN.)	PULSE RATE		T WAVE		BEFORE		S-T		AFTER		DIMINUTION OF T ₂ IN %	
				BEFORE	END	BEFORE	END	BEFORE	AFTER	BEFORE	END	BEFORE	AFTER	BEFORE	AFTER
<i>Age Group 15-20</i>															
M. B.	16	much	10	62	94	2	0	2	3½	0	0	0	0	100	
H. W.	17	average	11	54	115	4	½	2	3½	0	0	0	0	87 ½	
M. S.	17	little	12½	81	96	2½	½	2	3½	0	-1	0	0	80	
F. S.	18	average	10½	61	107	4	1¼	2	3¾	0	0	¾	¾	68 ¾	
D. S.	18	little	5½	83	107	2¼	1½	2	1½	0	0	0	0	33 ½	
F. T.	18	very	7	69	90	1½	0	1¾	1¾	-½	-1	-½	-½	100	
J. W.	18	very	10	75	143	3	0	1¾	1¾	-½	-1	-½	-½	100	
W. B.	19	much	10½	69	103	3	1½	3	1½	0	0	0	0	50	
E. B.	20	very	12½	100	125	1½	0	1½	1½	0	0	0	0	100	
H. B.	20	little	10½	90	103	3	2	3	3	0	0	0	0	33 ½	
<i>Age Group 20-30</i>															
A. H.	23	average	14½	62	90	5½	3	5	5	0	0	0	0	46	
L. F.	23	much	10½	90	125	3	½	3	3	0	0	0	0	83 ½	
M. H.	24	little	10	79	107	2	1¼	2	1¼	0	0	0	0	37 ½	
N. R.	24	much	8½	90	120	1½	¼	1¾	1¾	-½	-½	-½	-½	90	
A. K.	24	much	8	94	125	2	0	1¾	1¾	-½	-½	-½	-½	100	
A. L.	25	little	8	111	120	2½	1½	3½	3½	0	-½	0	0	40	
J. M.	25	much	11	61	111	3	1	2¼	2¼	-½	-½	0	0	60	
G. A.	26	little	11	85	103	3	1½	2¾	2¾	0	0	0	0	50	
W. M.	26	average	10	85	120	4	2	4	4	0	0	0	0	50	
C. Z.	28	much	10½	79	103	2½	½	2½	2½	0	0	0	0	80	

TABLE I—CONT'D

<i>Age Group 30-40</i>																			
M. S.	30	average	10½	77	103	77	1½	1½	1½	1½	1½	1½	0	0	0	0	0	0	0
F. P.	31	much	9	85	150	85	2	2	0	0	0	0	0	-1	0	0	0	0	100
R. R.	32	average	10½	79	107	79	3	3	1½	1½	3	2½	0	0	0	0	0	0	50
A. R.	33	little	6	83	107	83	2	2	1½	1½	2½	1½	0	0	0	0	0	0	37 ½
G. H.	34	much	12	66	94	66	2	2	1½	1½	2½	1½	0	-½	0	0	0	0	37 ½
F. H.	35	average	15½	75	107	75	2½	2½	1½	1½	2½	2½	0	0	0	0	0	0	40
E. J.	35	average	14½	55	96	55	2	1	1	1	2	2	0	0	0	0	0	0	50
M. H.	36	average	11	73	103	77	2	2	1½	1½	1½	1½	0	-¼	0	-¼	0	0	75
E. K.	37	average	10¼	57	107	62	4	2	2	2	2	2	0	0	0	0	0	0	50
E. W.	37	little	10½	85	103	85	1	1	1	1	1	1	-¼	-¼	-¼	-¼	0	0	0
<i>Age Group 40-50</i>																			
R. B.	41	little	10½	65	94	71	2¾	2	2	2	2	2	0	-½	0	0	0	0	27 ½
S. M.	41	average	9½	88	107	94	2¼	1½	1½	1½	2	2	0	0	0	0	0	0	33 ½
E. M.	41	little	9½	94	103	90	1½	1½	1½	1½	1½	1½	0	0	0	0	0	0	16 ¾
D. S.	41	average	15	68	77	62	4½	4½	4½	4½	4½	4½	0	0	0	0	0	0	0
E. L.	44	average	13	69	100	65	3	2	2	2	3	3	0	0	0	0	0	0	33 ½
N. L.	46	none	12	94	100	88	2¼	2¼	2¼	2¼	2¼	2½	0	0	0	0	0	0	0
W. M.	47	average	13	54	69	55	3	2½	2½	2½	3	3	0	0	0	0	0	0	16 ¾
M. F.	48	average	11	85	103	79	4	2½	2½	2½	3½	3½	0	0	0	0	0	0	37 ½
P. B.	49	average	10	79	94	79	2	1¼	1¼	1¼	2	2	0	0	0	0	0	0	37 ½
A. P.	49	average	11	79	94	88	1½	1½	1½	1½	1¾	1¾	0	0	0	0	0	0	0
<i>Age Group 50-70</i>																			
A. F.	52	average	9	90	103	100	3	2½	2½	2½	3	3	0	0	0	0	0	0	16 ¾
W. M.	53	average	11½	63	100	75	2	2	2	2	2½	2½	0	0	0	0	0	0	20
J. P.	55	average	11	75	83	71	2	1½	1½	1½	2	2	0	0	0	0	0	0	25
F. E.	55	average	11½	79	94	83	1½	1½	1½	1½	1½	1½	-¼	-¼	-¼	-¼	0	0	0
H. M.	55	little	11½	83	88	73	2½	2½	2½	2	3	3	0	0	0	0	0	0	20
E. P.	62	little	9	62	83	55	1½	1½	1½	1½	1½	1½	0	0	0	0	0	0	0
M. R.	63	average	12	88	107	96	1½	1½	1½	1½	1½	1½	0	0	0	0	0	0	33 ½
G. P.	65	none	9½	81	88	75	3	3	3	3	3	3	0	0	0	0	0	0	0
E. H.	65	much	9½	60	81	62	3	2	2	2	3	3	0	0	0	0	0	0	33 ½
R. S.	65	little	10½	68	100	69	1	7/8	7/8	7/8	1	1	-¼	-¼	-¼	-¼	-¼	-¼	12 ½

however, were found in all leads. The tendency to diminished response to oxygen deficiency, with advancing age, as measured roughly by changes in the height of the T wave, is very obvious (Fig. 9). Furthermore, there appears to be a striking correlation between the amount of bodily activity and decrease in the height of the T wave. Complete eradication of the T wave (100 per cent change) occurred exclusively in persons who were extremely active or in athletes.

TABLE II

AGE IN YEARS	% DECREASE IN HEIGHT OF T WAVE
15 to 20	75.3
20 to 30	63.7
30 to 40	49.0
40 to 50	20.2
50 to 70	16.1

This observation of the varying reaction in different age groups has, as far as the author is aware, not been made before. An indirect deduction can be made by comparing the classical tests made by Greene and Gilbert, and those made by Katz, Hamburger, and Schutz, in both cases on normal subjects. The former performed their experiments on members of the government aviation service, obviously younger people. The six curves published show almost complete eradication of T_2 near the end of the test, whereas in the latter study, which probably dealt with persons of various ages, only four out of sixteen showed a radical change.

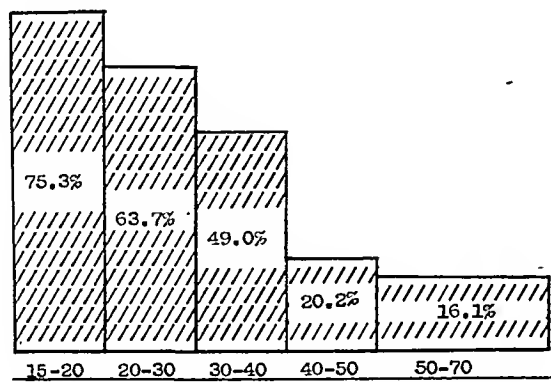


Fig. 9.—The average diminution of the height of T_2 , expressed in percentage, in the various age groups.

In summary, the following observations were made in fifty normal subjects.

1. Gradually induced anoxemia produces an acceleration of the heart rate, the degree of which varies individually.
2. Changes in the electrocardiogram coincide with the gradually decreasing oxygen intake, starting soon after the beginning of the experiment.

3. These changes are always of the same general nature; they consist of flattening, cradication, or, at times, inversion of the T wave, and occasionally depression of the S-T segment, and tend to occur in all three leads.

4. The electrocardiogram usually returns to normal within three to five minutes after the induction of anoxemia is stopped.

5. The effect of oxygen deficiency, as measured by diminution in the height of the T wave, lessens considerably with advancing age.

6. There seems to be a striking correlation between exercise tolerance and the degree of diminution in the height of the T wave.

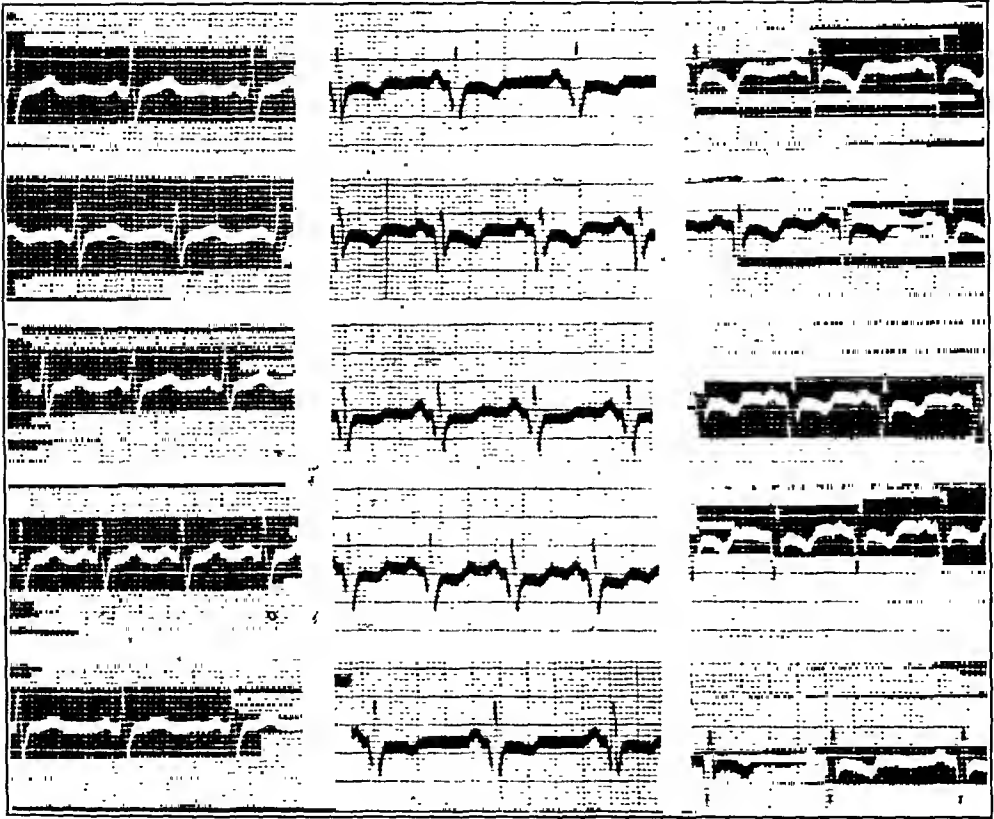


Fig. 10.—M. H. Age, 50. Electrolyst. 2½ years before, first attack of precordial pain, lasting a few minutes. Free of symptoms for 1 year. Never stopped working. Walks 10 blocks and more. Test: 8½ min. Discontinued because of heat in the head and dyspnea. First record, standard 3 leads. Second, third, and fourth records, 3, 5, and 8 min. after beginning to rebreathe. Last record, after 3 min. of breathing room air.

OBSERVATIONS ON PATIENTS WITH HEART DISEASE

The changes in the electrocardiogram following anoxemia induced in patients with heart disease are still under study, but a few observations might be included here. Of seven patients suffering from angina pectoris, none developed anginal pain at any time during the experiment. Of twenty experiments on patients with various types of heart disease, less than half have shown changes during periods of anoxemia, and only half of these are changes of major degree. The disease in the cases last mentioned was symptomatically mild. Several minutes after the

test was stopped, the electrocardiogram had often not returned to the previous state. Some changes noted in patients with heart disease had characteristics which seemed somewhat different from those seen in normal subjects. Whereas in normal subjects the changes followed the same tendencies in all three leads, in patients with heart disease they were at times more manifest in one lead than in the others in the successive records of an experiment (Fig. 10). From the literature,

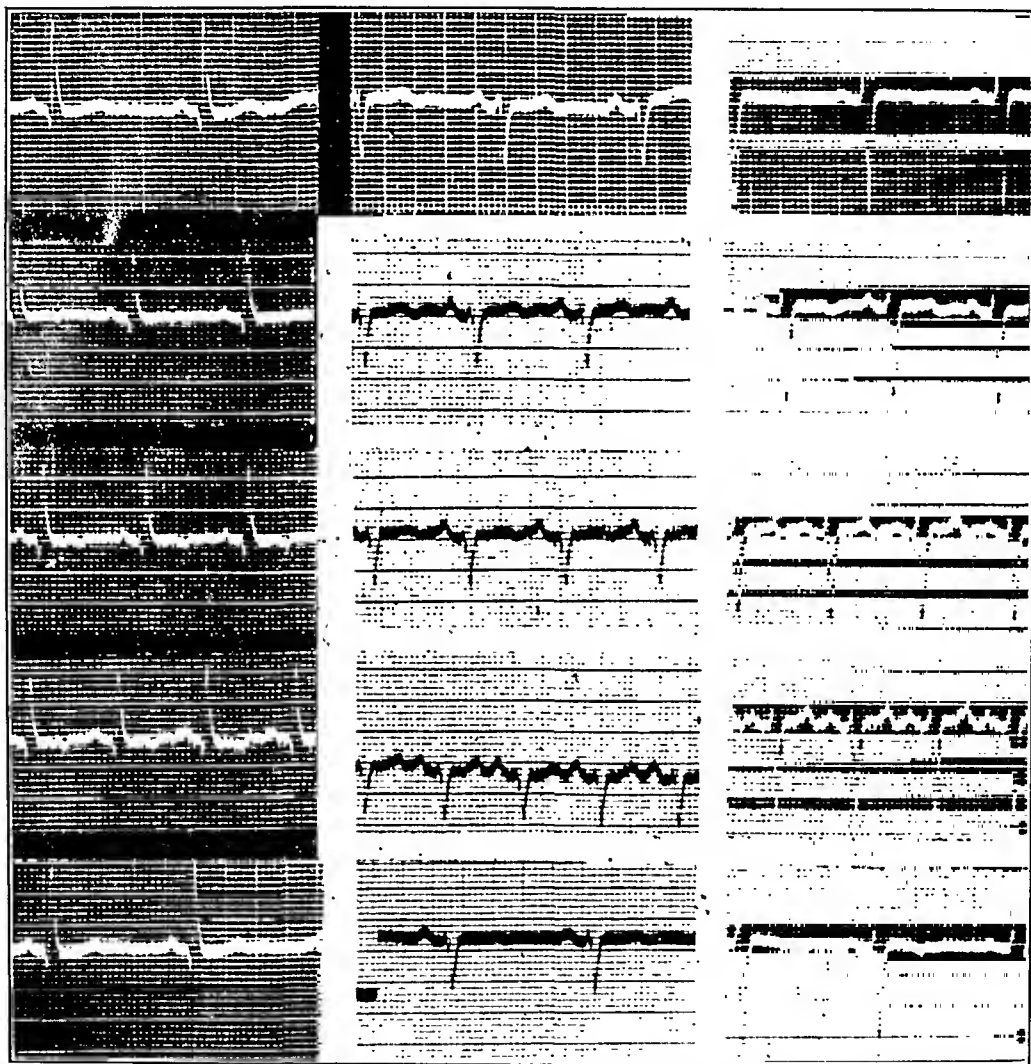


Fig. 11.—H. B. Age, 65. Formerly a salesman. Walks an average of 5 miles a day without discomfort. Blood pressure: 140/78. Test: $10\frac{1}{2}$ min. Discontinued because of shortness of breath. First record, standard 3 leads. Second, third, and fourth records, 3, 7, and 10 minutes after beginning to rebreathe. Last record after 3 min. of breathing room air.

as well as from my own observations, the impression obtained was that in experiments on persons whose intraventricular conduction time was delayed originally the changes during the experiment were of a relatively high degree but the deviation from the characteristics observed in the records of normal subjects was more marked.

One case, that of a 65-year-old man who had never complained of his heart, deserves comment (Fig. 11). The standard record showed a

slurred QRS complex, the duration of which was 0.11 second, exaggeration of the amplitude, and marked left axis deviation, and the T waves in Leads I and III were in the same direction as the QRS complexes. Surprisingly enough, during the course of the experiment the T waves altered their directions so that they came to lie opposite to the main deflection. (The shifting of the axis during the test occurred in all groups studied, but not in combination with the reversal of the direction of the T waves, as in this case.) This interesting observation suggests a possibility for the diagnosis of some types of intraventricular block in its early stages.

DISCUSSION AND COMMENT

The induction of gradually increasing anoxemia in all of the experiments performed, whether on normal subjects or patients with heart disease, was not accompanied or followed by any untoward effect. The symptoms of moderate discomfort which appeared near the end of the period of rebreathing disappeared instantly after the test was stopped. The complaints were mostly of shortness of breath, sensation of heat, and dizziness. Occasionally some aching in the arms and legs was described; some individuals complained of headache. None fainted or became unconscious. The fact that not one of seven patients with angina pectoris developed chest pain, a result which is different from that of other investigators, might be attributed to earlier discontinuation of anoxemia. Moderate discomfort was the signal for discontinuation. In one instance the experiment was stopped by the operator because cyanosis became more marked. This subject did not complain of any discomfort in spite of complete eradication of his T wave. It would appear, then, that with proper care there is no risk for the patient.

It may be added that experiments with vigorous breathing and exercise did not reproduce the changes observed during a period of anoxemia. Analysis of the successive records made during rebreathing, including records before and after, seems to provide new and promising possibilities for obtaining some idea concerning the intrinsic strength of the heart. I suggest that we call such a sequence of records the "an-oxygram," for purposes of abbreviation.

Two interesting facts emerge. The degree of change in the T wave decreases strikingly as age advances. It is also obvious that in athletic individuals the changes appear to be greater.

These observations seem to be contrary to the general notion of the significance of the T wave, since flattening of T waves is usually regarded as evidence of myocardial impairment. The fact that the highest degree of reduction in the height of the T wave during anoxemia occurs in young, athletic subjects suggests strongly that these great changes are associated with greater adaptability. Conversely, the lack or absence of change in older and enfeebled persons can be taken as indicative of their inability to compensate for lowered oxygen tension.

Of course, it might also be argued that the hearts of older persons, because of their frequent exposure to anoxemia, fail to react to the stimulus of decrease in oxygen tension. It becomes clear, from this discussion, that the precise mechanism which leads to the changes in the T wave is imperfectly understood. Regardless of theoretical considerations, however, the practical evaluation of changes in the T wave during anoxemia and the effect of age and physical endurance on these changes are clear.

The result of the experiments on persons with normal hearts provides evidence that the degree of T wave changes during periods of induced anoxemia may be useful as an appropriate measure of the functional capacity of the cardiac muscle.

SUMMARY

1. The effect on the electrocardiogram of anoxemia induced by re-breathing was studied.

2. It was found that in persons with normal hearts anoxemia produced uniformly and progressively in all three leads a flattening of the T wave and occasionally a depression of the S-T segment.

3. The degree of the T wave flattening was found to be very high in young subjects. It diminished greatly with advancing age. In the subjects between fifteen and twenty years of age, the average percentage of the diminution of T_2 was 75.3 per cent; in those between twenty and thirty, 63.7 per cent; between thirty and forty, 49 per cent; between forty and fifty, 20.2 per cent; and between fifty and seventy years of age, 16.1 per cent.

4. There was also a striking correlation between the amount of bodily activity and the degree of electrocardiographic change. Complete eradication of the T wave was seen only in very active or athletic young people.

5. The results of these observations were discussed from theoretical and practical points of view. Electrocardiograms made before, during, and after re-breathing would appear to be valuable in testing the functional capacity of the cardiac muscle.

REFERENCES

1. Greene, C. W., and Gilbert, N. C.: Studies on the Responses of the Circulation to Low Oxygen Tension. III. Changes in the Pacemaker and in Conduction During Extreme Oxygen Want as Shown in the Human Electrocardiogram, *Arch. Int. Med.* 27: 517, 1921.
2. Rothschild, M. A., and Kissin, M.: Production of the Anginal Syndrome by Induced General Anoxemia, *AM. HEART J.* 8: 729, 1932-1933.
3. Rothschild, M. A., and Kissin, M.: Induced General Anoxemia Causing S-T Deviation in the Electrocardiogram, *AM. HEART J.* 8: 745, 1932-1933.
4. Katz, L. N., Hamburger, W. W., and Schutz, W. J.: The Effect of Generalized Anoxemia on the Electrocardiograms of Normal Subjects. Its Bearing on the Mechanism of Attacks of Angina Pectoris, *AM. HEART J.* 9: 771, 1933-1934.
5. Levy, R. L., Barach, A. L., and Bruenn, H. G.: Effects of Induced Oxygen Want in Patients With Cardiac Pain, *AM. HEART J.* 15: 187, 1938.

THE SIGNIFICANCE OF RHEUMATIC ACTIVITY IN CHRONIC RHEUMATIC HEART DISEASE*

PART II. A METHOD OF CLASSIFICATION

IRVING R. JUSTER, M.D.

GLENS FALLS, N. Y.

ONE of the factors causing cardiac dysfunction in adults with rheumatic cardiac disease is the persistence of prolonged and progressive active infection, sometimes so mild as scarcely to be detectable, especially during symptomless periods.¹ Insufficient use of more specific means for ascertaining the degree of rheumatic activity has resulted in inadequate knowledge concerning the course of the disease, particularly in the chronic form encountered in rheumatic cardiac affection.

Since the degree of rheumatic activity varies, even when of low grade, from discontinuous to continuous,¹ a classification was adopted for the purpose of ascertaining the degree. Leucocytosis was chosen as the criterion because it occurs both when the cardiac rhythm is normal and in the presence of auricular fibrillation, and because of the simplicity of the technique of counting leucocytes and a knowledge of the normal range of the leucocyte count.^{1, 2}

Although the amount of leucocytosis is indicative of the severity of the infection in acute polyarthritis,^{8, 9} the continued presence of any leucocytosis is more significant of the chronic form.¹

METHOD OF CLASSIFICATION

In patients in whom the deviations from a normal leucocyte count (below 9,000 cells) were 10 per cent, or less, the disease was considered as being inactive; the remainder were divided into three groups, depending on the amount of the deviation. In any case the degree

TABLE I
CLASSIFICATION OF RHEUMATIC ACTIVITY

	PERCENTAGE OF TOTAL NUMBER OF LEUCOCYTE COUNTS ABOVE 9,000
Inactive	0- 10 per cent
First degree activity	11- 40 per cent
Second degree activity	41- 70 per cent
Third degree activity	71-100 per cent

Received for publication Nov. 7, 1938.

*This is the third article on investigations undertaken at the New York Cardiac Shop, conducted under the auspices of the Committee on Cardiac Clinics of the New York Heart Association. This study was made possible by grants from the Hofheimer Foundation for three years, the New York Foundation for two years, and the Altman Foundation for one year. The remainder of the fund was subscribed by the Board of Directors of the New York Cardiac Shop. This Board was created by the Board of Directors of Irvington House.

of abnormality depended on the percentage of abnormal to the total number of counts (Table I). For example, a patient exhibiting abnormal leucocyte counts to the extent of 50 per cent of his total number of counts would be classified as second degree, 80 per cent as third

TABLE II

RANGE OF THE LEUCOCYTE COUNTS AND AVERAGE LEUCOCYTE COUNTS IN EACH CASE

CASE NO.	AGE	FUNCTION- AL CLASS.	RHYTHM	LOWEST	HIGHEST	AVERAGE
Inactivity						
3. E. B.	17	IIA	RSR*	4,300	11,900	7,200
8. C. B.	30	IIB	AF†	4,600	11,300	6,900
16. B. G.	16	IIA	RSR	4,400	11,300	6,900
18. F. G.	17	IIB	RSR	4,100	10,600	7,000
22. W. H.	40	IIA	RSR	5,200	8,800	7,200
28. I. L.	21	IIB	RSR	4,100	6,900	5,400
38. E. P.	17	IIB	RSR	4,500	8,300	6,400
41. J. P.	24	IIB	RSR	5,200	6,000	5,600
53. M. So.	24	IIB	AF	6,000	9,000	7,800
Group Average		22.9 years		4,700	9,300	6,700
First Degree Activity						
2. T. A.	15	IIB	RSR	4,300	12,200	8,600
4. B. Ba.	17	IIA	AF	7,500	12,400	9,400
5. B. Bn.	15	IIA	RSR	5,100	12,400	8,500
9. S. B.	30	IIB	RSR	3,200	10,600	7,800
11. E. C.	17	IIB	RSR	4,400	12,000	7,800
24. C. H.	18	IIB	AF	5,100	10,800	7,800
31. B. M.	19	IIB	RSR	4,800	13,600	7,800
33. M. My.	21	IIB	RSR	4,500	15,000	8,000
43. S. R.	23	IIB	RSR	6,500	12,400	8,700
44. R. R.	36	IIB	AF	5,200	12,000	7,900
49. Ia. S.	28	IIB	AF	4,200	11,800	7,800
52. H. S.	16	IIB	RSR	4,500	15,600	8,300
55. G. S.	23	IIA	RSR	4,000	16,500	7,500
56. I. Sh.	27	IIA	RSR	3,000	14,500	8,000
57. M. Sk.	44	IIB	AF	3,800	15,700	7,300
58. Hl. S.	17	IIA	AF	3,600	14,800	7,800
Group Average		22.9 years		4,600	13,000	8,100
Second Degree Activity						
7. S. B.	17	IIB	RSR	5,000	17,000	10,100
10. M. C.	22	IIA	RSR	7,900	11,700	9,600
12. J. D.	18	IIA	AF	5,600	14,700	10,100
13. L. D.	17	I	RSR	6,300	11,800	9,400
15. N. F.	21	IIB	RSR	4,700	17,200	9,600
19. D. G.	18	IIB	RSR	5,600	14,600	9,400
23. F. Hs.	17	IIB	RSR	4,100	17,500	9,100
25. S. Ky.	16	IIB	RSR	4,600	17,100	10,100
32. E. My.	22	IIB	RSR	6,600	16,700	10,000
37. A. O.	16	IIA	RSR	7,000	10,900	9,300
39. C. P.	18	IIB	AF	5,000	15,400	9,200
46. R. S.	17	IIB	RSR	4,700	14,000	8,900
50. J. S.	26	IIB	RSR	5,700	15,400	10,000
51. Je. S.	20	IIB	AF	4,800	14,400	9,400
54. D. S.	17	IIB	RSR	4,100	12,100	7,600
Group Average		19 years		5,400	14,700	9,500

*Regular sinus rhythm.

†Auricular fibrillation.

TABLE II—CONT'D

CASE NO.	AGE	FUNCTION- AL CLASS.	RHYTHM	LOWEST	HIGHEST	AVERAGE
<i>Third Degree Activity</i>						
1. P. A.	16	IIB	RSR	7,900	19,900	13,100
6. H. B.	19	IIB	RSR	5,100	18,100	10,600
14. J. E.	31	IIB	RSR	9,200	12,200	11,300
17. H. G.	17	IIA	RSR	10,000	13,200	11,700
20. A. G.	25	IIB	AF	10,000	15,200	12,300
21. F. Hr.	20	IIB	RSR	9,100	10,300	9,900
26. R. K.	30	IIB	AF	5,800	12,400	9,500
27. S. Km.	24	IIA	RSR	7,700	17,000	12,600
29. R. L.	20	IIB	RSR	5,600	18,000	10,700
30. E. L.	17	IIA	RSR	4,900	22,100	11,500
34. E. Mz.	25	IIB	RSR	10,200	16,200	14,200
35. M. Ma.	17	IIB	RSR	9,000	14,700	11,300
36. J. O.	16	IIB	AF	6,200	19,900	11,500
40. M. P.	19	IIB	RSR	6,900	13,000	10,200
42. P. P.	17	IIB	RSR	6,000	17,000	10,200
45. A. R.	28	IIB	AF	11,800	16,200	13,700
47. M. Sr.	17	IIB	RSR	9,100	13,900	11,800
48. E. S.	17	IIB	RSR	7,100	13,700	10,200
59. E. Z.	18	IIB	RSR	7,100	18,500	11,400
Group Average		20 years		7,900	16,100	11,500

degree, and so on. By this means, the disease was classed as inactive in 9 cases, and as active in the first degree in 16, in the second degree in 15, and in the third degree in 19.

The range and the average of the leucocyte counts in each case exhibited progressive increases from the stage of inactivity to the third degree (Table II, Fig. 1). On the average, patients exhibiting inactivity and activity of the first degree were somewhat older (3 to 4 years) than those with activity of the second and third degree.

In order to test the value of this method of classification, it was checked with other criteria of rheumatic activity. For this purpose the temperature and pulse rate (in patients with normal rhythm) were selected and the percentage that were abnormal was estimated

TABLE III

COMPARISON OF OTHER CRITERIA OF RHEUMATIC ACTIVITY WITH THE VARIOUS DEGREES OF ACTIVITY OBTAINED BY THE CLASSIFICATION

	ABNORMAL LEUCOCYTE COUNTS	ABNORMAL TEMPERATURE	ABNORMAL PULSE RATES (RSR*)	TRANSIENT ABNOR- MALITIES IN ELECTROCARDIOGRAMS	ADDITIONAL NEW VALVE LESIONS	ACUTE CARDITIS	CARDIAC DEATHS
Inactivity	5.4%	6.6%	29.5%	14.0%	22.0%	22.0%	22.0%
First degree activity	24.4%	7.7%	26.2%	60.0%	0.0%	25.0%	41.0%
Second degree activity	56.6%	9.5%	40.6%	67.0%	26.4%	13.3%	33.0%
Third degree activity	81.0%	15.4%	53.5%	77.0%	31.6%	42.1%	53.0%

*Regular sinus rhythm.

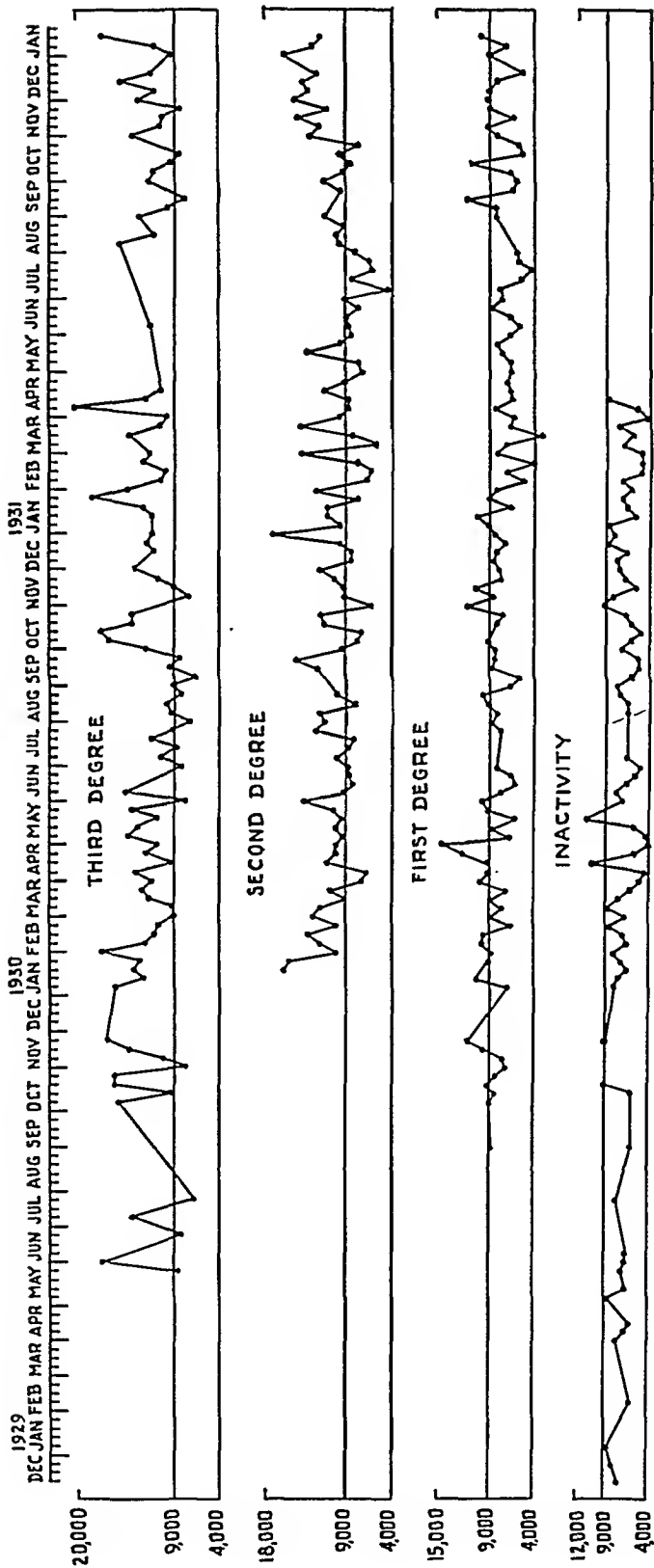


Fig. 1.—Leucocyte curves of representative cases in each degree of activity.

(Table III). Transient changes in the electrocardiograms, the development of new valvular lesions, the presence of acute carditis, and the percentage of deaths attributed to cardiac disease were also studied (Table III). The result suggests an increase in the severity of rheumatic activity parallel with the leucocyte count index.

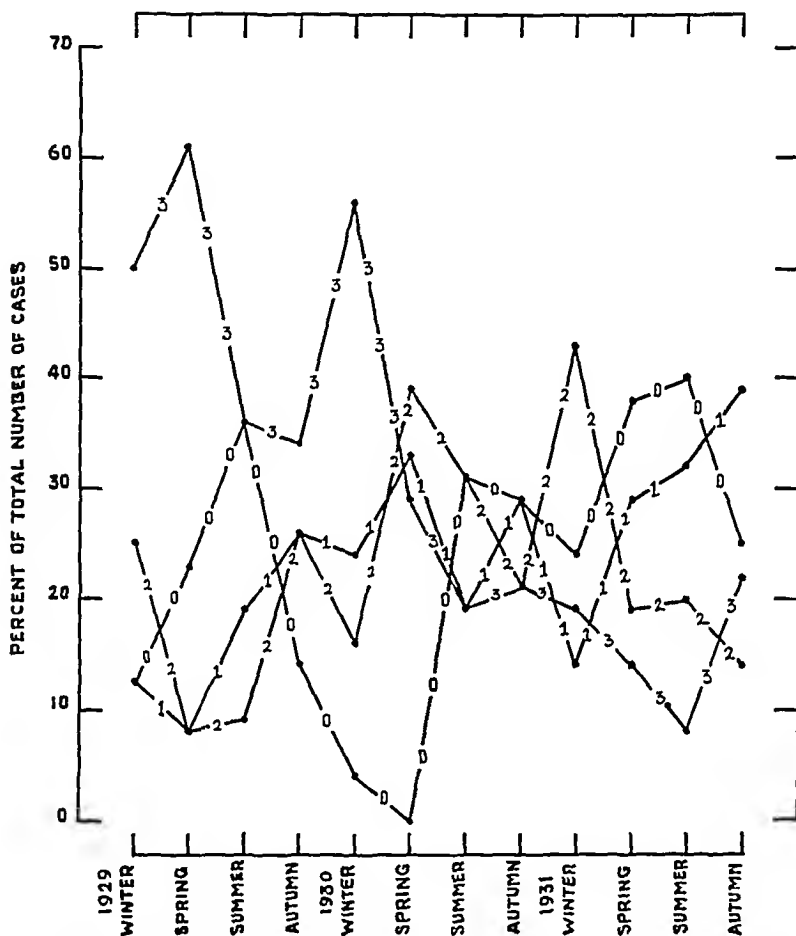


Fig. 2.—Seasonal variations of the degrees of activity. The numerals 0, 1, 2, 3, which interrupt the curves, serve to identify the classes and to make possible tracing the course of the curves.

APPLICATION OF CLASSIFICATION

Whether or not a change in the degree of severity took place with changes in the season of the year has been studied. In Cases 3 and 8, in which the disease had been classified as inactive (Table IV), activity first appeared during the summer of 1931 (Case 3) and the spring of 1930 (Case 8). In most cases of first degree activity cyclic periods of activity and quiescence occurred, whereas quiescence was only occasional in the second and third degree groups. It was interesting to observe the gradual shift of the degree of activity from season to season, increasing or decreasing by single stages, rarely abruptly by more. This phenomenon is important because it depicts the fact that rheu-

matic activity may develop or recede slowly in the absence of signs and symptoms. During the winter of 1932 four patients (Case 53, first degree; Cases 25 and 51, second degree; Case 36, third degree, Table IV) manifested activity of the third degree as exhibited by their leucocyte counts, but had a normal cardiac reserve (Functional Classification I). All of the patients with obvious evidence of acute carditis showed evidence of pre-existing rheumatic activity.¹ Although cardiac damage (acute carditis) was more apparent in patients with leucocyte counts of the third degree, it was equally serious but more insidious in its development in those with counts of lesser degrees. Viewed seasonally, diminished cardiac function was found sometimes to occur, therefore, with decreasing rheumatic activity. This was particularly noticeable in patients with long-continued auricular fibrillation.

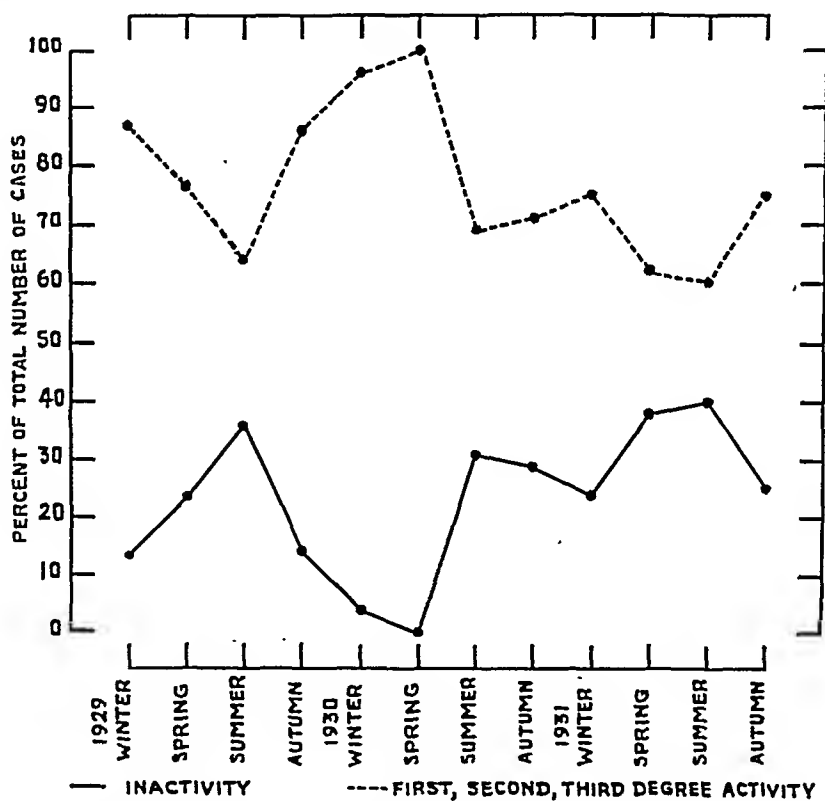


Fig. 3.—Seasonal variation of rheumatic activity based on abnormal leucocyte count percentages; first, second, and third degrees combined and compared with inactivity.

SEASONAL VARIATION OF DEGREE OF RHEUMATIC ACTIVITY

The least activity, according to this classification (leucocytosis), occurred during the summer, but the peak did not always occur in the same season. In 1929 it was in the winter, in 1930 in the spring, and in 1931 in the winter (Figs. 2 and 3). These findings are in accord with those of other observers, though this study was based on leucocyte counts and theirs on clinical manifestations.^{3, 4, 5, 6, 7}

TABLE IV
SEASONAL RELATIONSHIP OF DEGREE OF ACTIVITY AND FUNCTIONAL CLASSIFICATION

CASE	1929				1930				1931				1932	
	WINTER	SPRING	SUMMER	FALL	WINTER	SPRING	SUMMER	FALL	WINTER	SPRING	SUMMER	FALL	WINTER	WINTER
<i>Inactivity</i>														
3. E. B. RSR*											1 IIB-IIA	0 IIA	0 IIA-I	
8. C. B. AF†	0‡ IIB-III§	0 III-IIB	0 IIB	0 IIB-III	0 IIB	1 IIB-III	0 IIB	0 IIB	0 IIB	0 IIB				
16. B. G. RSR							0 IIB	0 IIB-III	0 IIB					
18. F. G. RSR										0 IIB	0 IIB	0 IIB-IIA	0 IIA	
22. W. H. RSR		0 IIA	0 IIA	0 IIA										
28. I. L. RSR											0 IIB-IIA	0 IIA		
38. E. P. RSR											0 IIB	0 IIB-IIA	0 IIA-I	
41. J. P. RSR										0 IIB				
52. M. S. AF											0 IIB-III	0 IIB		

*Regular sinus rhythm.

†Auricular fibrillation.

‡The upper, Arable, numerals designate the degree of activity.

§The lower, Roman, numerals designate the functional classification and fluctuations when showing more than one figure.

TABLE IV—CONT'D

CASE	1929			1930			1931			1932	
	WINTER	SPRING	SUMMER	FALL	WINTER	SPRING	SUMMER	FALL	WINTER	FALL	WINTER
<i>First Degree Activity</i>											
2. T. A. RSR									2 IIB	1 IIB-IIA	
4. B. Ba. AF									1 IIA-IIB		
5. B. Bn. RSR									1 IIA-I	1 I	
9. S. B. RSR										1 IIB	
11. E. C. RSR									1 IIB-IIA	1 IIA	0 IIA
24. C. H. AF									1 IIB	1 IIB-III	
31. B. M. RSR									0 IIB	0 IIB	
33. M. M. RSR									1 IIA	1 IIA	2 I
43. S. R. RSR											
44. R. R. AF			0 IIB-IIA	1 IIB-IIA	1 IIA	2 IIA-IIB					
49. I. S. AF		0 IIB-III	1 IIB-IIA	1 IIB	1 IIB	0 IIB	1 IIA-IIB	0 IIB-IIA	0 IIB	1 IIB	1 IIB
53. H. S. RSR									0 IIB-IIA	1 IIA-I	3 I
55. G. S. RSR		2 IIA-IIB	0 IIB-IIA	1 IIB-IIA	1 IIA	0 IIA	0 IIA-IIB	0 IIB-IIA	0 IIA	0 IIA	0 IIA
56. I. Sh. RSR			1 IIA-IIB	1 IIB	2 IIA	1 IIA	0 IIA	0 IIA-IIB	0 IIA-IIB	1 IIA	1 IIA
57. M. S. AF					1 IIB	0 IIB-IIB	1 IIB	1 IIB			
58. H. S. AF		1 IIA-IIB		0 IIA	1 IIB-IIA	0 IIB-IIA	0 IIA-IIB	0 IIA-IIB			

See legend, Table IV, first section.

TABLE IV—CONT'D

CASE	1929				1930				1931				1932	
	WINTER	SPRING	SUMMER	FALL	WINTER	SPRING	SUMMER	FALL	WINTER	SPRING	SUMMER	FALL	WINTER	WINTER
<i>Second Degree Activity</i>														
7. S.B. RSR	3 IIB-IIA	3 IIB	1 IIB	2 IIB	3 IIB-IIA	2 IIA-IIB	2 I-IIA	1 IIA-I						
10. M.C. RSR			3 IIA	3 IIA-IIB	3 IIA-IIB	3 IIA	2 IIA	3 IIA	2 IIA	1 IIA-IIB	2 IIB-IIA		2 IIA	
12. J.D. AF														3 IIA
13. L.D. RSR												2 I	2 I-IIB	
15. N.F. RSR	3 IIB	3 IIB	1 IIB	1 IIB	3 IIB	2 IIB-IIB	1 IIB	1 IIB-IIA	2 IIB-IIA	2 IIB				
19. D.G. RSR												2 IIB-II	1 IIA-I	
23. F.H. RSR					3 IIB-IIA	3 IIB-IIA	3 IIA-IIB	2 IIA-I	2 IIA-IIB	1 I-IIA	0 IIA	1 IIA-I	2 I	
25. S.K. RSR					3 IIB	3 IIB-IIA	2 IIA-IIB	2 IIB-IIA	2 IIB-IIA	2 IIA-IIB	1 IIA-IIB	3 IIA	3 IIA-I	
32. E.M. RSR								3 IIB-IIA	2 IIA-IIB					
37. A.O. RSR												2 IIB-IIA		
39. C.P. AF		3 IIA-IIB	3 IIB-IIA	2 IIA-IIB	2 IIB-IIA	2 IIA	2 IIA	0 IIA	2 IIA	0 IIA				
46. R.S. RSR				1 IIB	1 IIB	2 IIB	2 IIB-IIA	1 IIA	2 IIA	2 IIA	1 IIA	3 IIA	2 IIA	
50. J.S. RSR					2 IIB-IIA	2 IIB-IIA								
51. I.C. AF								2 IIB-IIA	2 IIB-IIA	2 IIA-I	2 IIA-I	2 IIA-I	3 I	
54. D.S. RSR				2 IIB-IIA	1 IIA-IIB	1 IIB-IIA	0 IIA-IIB	1 IIA-IIB	1 IIA-IIB	0 IIA-IIB		1 IIA-I	0 I	

See legend, Table IV, first section.

TABLE IV—CONT'D

CASE	1929				1930				1931				1932	
	WINTER	SPRING	SUMMER	FALL	WINTER	SPRING	SUMMER	FALL	WINTER	SPRING	SUMMER	FALL	WINTER	WINTER
<i>Third Degree Activity</i>														
1. P. A. RSR	3 IIB-III	3 III			3 IIB-III		3 IIB-III		3 IIB	3 IIB-III				3 IIB
6. H. B. RSR	2 IIB-IIA	3 IIA-IIB	3 IIA	2 IIB-III		2 IIB-III					2 IIB			
14. J. E. RSR					3 IIB									
17. H. G. RSR		3 IIB-III												
20. A. G. AF		3 IIB												
21. F. H. RSR				3 IIB-III										
26. R. K. AF												3 IIB	2 IIB	
27. S. K. RSR				3 IIA	3 IIA-IIB	3 IIA								

See legend, Table IV, first section.

29.	R. L. RSR	2 IIB-IIA	3 IIA-IIB	3 IIB	3 IIB	3 IIB-IIA	3 IIB-IIA	3 IIB	3 IIB-III	3 IIB-IIA	3 IIB		3 IIB-IIA		3 IIA
30.	E. L. RSR									2 IIA-IIB	3 IIB				
34.	E. M. RSR		3 IIB-III												
35.	M. M. RSR												3 IIB		
36.	J. O. AF			2 IIB-III	3 IIB-IIA	3 IIB-IIA	3 IIA-IIB	1 III-IIB	3 IIB-III	3 IIA-IIB	3 IIB-III	3 IIB-IIA			3 I
40.	M. P. RSR	1 IIB			3 IIB	3 IIB									
42.	P. P. RSR				3 IIB	3 IIB	2 IIA-IIB								
45.	A. R. AF				3 IIB-III										
47.	M. S. RSR	3 IIB													
48.	E. S. RSR					3 IIB	2 IIB	2 IIB-III	3 IIB-III						
59.	E. Z. RSR				3 IIB-III	3 IIB-III	3 IIA	3 IIA							

SUMMARY

1. A method of separating patients with active rheumatic heart disease into classes of increasing degrees of activity is described. It is based on the percentage of abnormal leucocyte counts in each case. Patients placed in the inactive group comprise those whose counts were within the normal range. In nine cases the disease was classified as inactive, in sixteen as active in the first degree, in fifteen as active in the second degree, and in nineteen as active in the third degree.

2. Beginning with the inactive group and proceeding through the groups of first, second, and third degree activity, there was progressive increase in the range and in the average leucocyte counts.

3. The average age of the patients in the inactive and first degree groups was higher than that in the second and third.

4. Using the criteria tested in this study, it was found that rheumatic activity was more intense in patients in the third degree group and least in those in the inactive group.

5. The activity of the rheumatic process was least during the summer of each year.

6. Fluctuation in the degree of activity, according to the classification, was very gradual, usually one degree at a time. Since most acute manifestations of rheumatic activity occurred in the higher degree groups, a pre-existing active phase of a lower degree was usually present. Evidence is adduced to show that there are symptomless periods in patients with third degree activity.

CONCLUSION

Using the leucocyte count as a basis of classification it has been found useful and instructive to divide cases of rheumatic activity into four groups: inactive, first, second, and third degrees, respectively.

REFERENCES

1. Juster, I. R.: Significance of Rheumatic Activity in Chronic Rheumatic Heart Disease, *AM. HEART J.* 15: 1, 1938.
2. Juster, I. R.: The Normal Range of the Leucocyte Count Determined Weekly Over an Extended Period, *J. Lab. & Clin. Med.* 21: 376, 1936.
3. Findlay, L.: *Rheumatic Infection in Childhood*, London, 1931, William Wood & Co.
4. Coburn, A. F.: *The Factor of Infection in the Rheumatic State*, Baltimore, 1931, The Williams & Wilkins Co.
5. Swift, H. F.: Rheumatic Fever, *Nelson's Loose Leaf Medicine* 1: 401, 1931.
6. Paul, J. R.: *The Epidemiology of Rheumatic Fever*, For American Heart Association, Metropolitan Life Insurance Company, 1930.
7. Wilson, M. G., Ingerman, E., Du Bois, R. O., and Spock, B.: The Relation of Upper Respiratory Infection to Rheumatic Fever in Children, *J. Clin. Investigation* 14: 325, 1935.
8. Swift, H. F., Miller, C. P., and Boots, R.: *J. Clin. Investigation* 1: 197, 1924.
9. Ernste, A. C.: *Am. J. M. Sc.* 180: 12, 1930.

RIGHT VENTRICULAR HYPERTROPHY AND CONGESTIVE FAILURE IN CHRONIC PULMONARY DISEASE

DONALD E. GRIGGS, M.D., CHARLES B. COGGIN, M.D., AND

NEWTON EVANS, M.D.

LOS ANGELES, CALIF.

RIGHT ventricular failure is an important cause of death in chronic pulmonary disease. Chronic cor pulmonale (chronic pulmonary heart disease) is often considered such a rarity that the diagnosis is overlooked or made with great hesitancy in these cases. Chronic cor pulmonale is caused by hypertension in the pulmonary circulation which results from disease of the lungs or its blood vessels. It is characterized pathologically by hypertrophy of the right ventricle and, when the heart fails, by signs of systemic venous congestion. Congestive failure occurs late in the course of the disease.

We have undertaken to ascertain the incidence of cor pulmonale in the more common chronic pulmonary diseases. Inasmuch as the clinical diagnosis of this condition is often unreliable, we base our conclusions on the study of autopsy material in which the pulmonary and cardiac lesions can be clearly recognized and evaluated.

MATERIAL

We reviewed the protocols of all chronic pulmonary lesions listed in the cross index of the 18,000 autopsies done at the Los Angeles County Hospital during the past nineteen years. Cases in which the pulmonary lesions were described as minimal or localized, obviously incapable of affecting the pulmonary circulation, were excluded from our study.

We found that many patients had more than one pulmonary disease and some had heart disease other than cor pulmonale. To evaluate the effect of each pulmonary disease upon the heart we divided the total number of cases of each pulmonary disease into the following groups: (1) Cases in which the patients had only the one pulmonary disease and had no cardiac lesion other than cor pulmonale, hereafter designated as cases "alone"; (2) cases in which the patients had additional pulmonary lesions but no cardiac disease other than cor pulmonale, designated hereafter as "associated pulmonary" cases; (3) cases in which the patients had only the single pulmonary lesion but had cardiac disease other than cor pulmonale, including those with high blood pressure (150/100 or more), designated in this paper as "cardiac" cases (we

From the Departments of Medicine and Pathology, College of Medical Evangelists and the Los Angeles County Hospital.

Read before the Section on Practice of Medicine at the Annual Session of the American Medical Association, San Francisco, Calif., June 15, 1938.

Received for publication Nov. 13, 1938.

have entirely excluded from our study the few cases of mitral disease and congenital heart disease which would primarily cause right ventricular hypertrophy); (4) cases in which the patients had both additional pulmonary lesions and had cardiac disease other than the chronic pulmonary heart disease, designated as “associated pulmonary and cardiac” cases (see Fig. 2).

CRITERIA

Estimation of right or left ventricular hypertrophy is most accurately accomplished by weighing each ventricle separately.¹ Since only cardiac weights and mural thicknesses had been recorded by the autopsy surgeon, we were obliged to use the average thickness of the ventricular wall as the criterion of hypertrophy. Hearts in which the right and left ventricular walls measured less than 4 mm. and not more than 12 mm., respectively, in average thickness were considered normal. A right ventricular wall which averaged 5 mm., or a left ventricular wall which averaged over 15 mm. in thickness, was considered definitely hypertrophied. The term “hypertrophy of both ventricles” was used to designate hearts in which both right and left ventricles were definitely hypertrophied, and also hearts in which the wall of the right ventricle

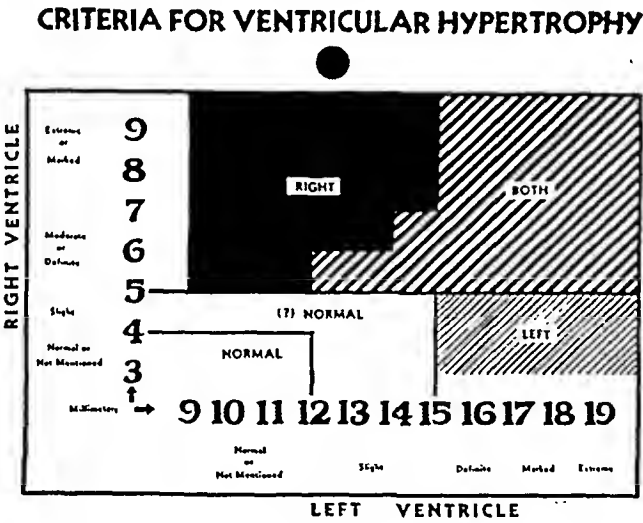


Fig. 1.

was 5 to 6 mm. and the left more than 12 mm. in thickness, or the wall of the right ventricle 6 to 7 mm. and that of the left more than 14 mm. Our criteria, therefore, restrict the term “right ventricular hypertrophy” to those hearts which have a *predominant* right ventricular hypertrophy (Fig. 1, solid black area). Although Thompson and White² found that left ventricular strain was the greatest cause of right ventricular hypertrophy, the great majority of their examples of right ventricular hypertrophy would have been listed, by our criteria, under “hypertrophy of both ventricles” (Fig. 1, heavy shaded area). We believe that the percentage of right ventricular hypertrophy in the group of cases “alone” (cases in which the patient had only one pulmonary

disease and no cardiac disease other than cor pulmonale) represents quite conservatively the incidence of cor pulmonale caused by the lesion under discussion.

Our classification still leaves a small group of hearts with questionable hypertrophy of the right or left ventricle which we classed as "questionably normal." In some autopsy records, the thickness of the right ventricle or, rarely, of the left ventricle, was not stated. If not mentioned, we have considered the ventricle as normal. This added an unavoidable error, but one which would minimize and not overemphasize the effect of the chronic pulmonary diseases studied as causes of cor pulmonale. Rarely the ventricles were not measured but described as "slightly," "moderately," or "greatly hypertrophied." Fig. 1 will visualize the criteria used in this study.

The term "definite congestive failure" was reserved for patients who showed marked chronic passive congestion of the liver, associated with either ascites or edema, or with a pathologist's diagnosis of "congestive failure." All cases in which the evidence was less convincing, but suggestive, were classed as "questionable failure."

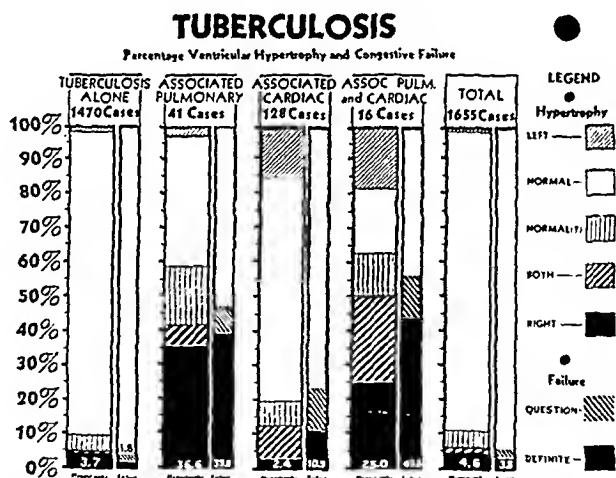


Fig. 2.

RESULTS

Chronic Bronchitis.—In 92 of 185 cases of chronic bronchitis the lungs showed no other pulmonary lesions. In this group we found no case of right ventricular hypertrophy or congestive failure which we felt was caused by the chronic bronchitis. We have, therefore, disregarded the incidental diagnosis of chronic bronchitis in the study of the other pulmonary diseases.

Pulmonary Tuberculosis.—Among the 18,000 autopsies there were 1,655 cases (9.1 per cent) of moderately or far-advanced pulmonary tuberculosis.

In the total of 1,655 cases, approximately 86.8 per cent of the hearts showed no ventricular hypertrophy, while only 4.6 per cent showed

"right ventricular hypertrophy." If, to this 4.6 per cent, are added the cases in which the right ventricle was slightly hypertrophied, but with a mural thickness of less than 5 mm., and the cases in which both ventricles were hypertrophied, the total incidence of right ventricular hypertrophy is still only 10.2 per cent. These figures differ greatly from those recently reported by Nemet and Rosenblatt,³ who found exclusive hypertrophy of the right ventricle in 33.8 per cent of 71 cases of tuberculosis. Including the cases with hypertrophy of both ventricles, the right ventricle was hypertrophied in 46.5 per cent of their total group.

In 1,470 cases of tuberculosis "alone," we found that 3.7 per cent of the hearts were the seat of pure right ventricular hypertrophy, while 90.8 per cent showed no hypertrophy. We were unable to correlate the cardiac hypertrophy with specific types of tuberculosis, although, of course, it was generally found in advanced cases. In 41 cases with "associated pulmonary" lesions in which pneumoconiosis frequently occurred, the percentage of right ventricular hypertrophy increased to 36.6 per cent, pointing conclusively to the fact that tuberculosis falls far below the average of other chronic pulmonary diseases, especially pneumoconiosis, as a cause of right ventricular hypertrophy (Fig. 2).

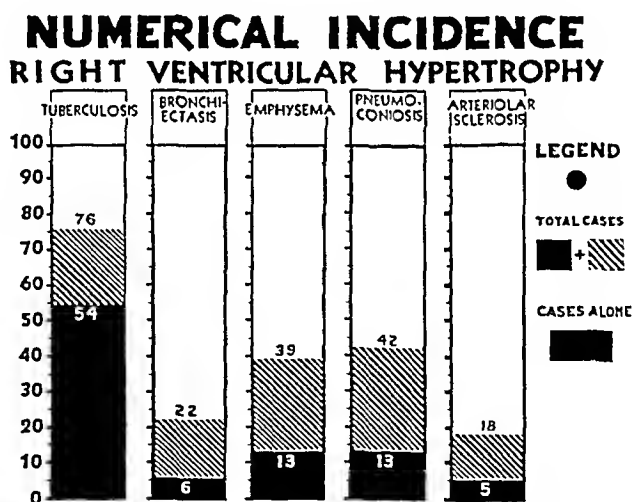


Fig. 3.

The tuberculosis group had the lowest *percentage* of right ventricular hypertrophy of all chronic pulmonary disease groups, except chronic bronchitis. Nevertheless, due to the high incidence of tuberculosis, right ventricular hypertrophy was seen more frequently at autopsy in patients with tuberculosis than with any other pulmonary disease (Fig. 3).

Of the total of 1,655 patients with tuberculosis, there were 3.8 per cent with definite failure and 2.8 per cent with questionable failure, totaling 6.6 per cent. Among the 1,470 patients with pulmonary tuberculosis "alone," 1.8 per cent had definite congestive failure and 1.8 per cent had questionable failure, totaling 3.6 per cent (Fig. 2).

Bronchiectasis.—Bronchiectasis of moderate or marked degree was found in 136 cases. Right ventricular hypertrophy occurred in 16.2 per cent of these patients. In the 68 patients with bronchiectasis “alone,” 8.8 per cent showed pure right ventricular hypertrophy, while 82.4 per cent showed no hypertrophy of either ventricle. This was over twice the percentage of right ventricular hypertrophy found in patients with tuberculosis “alone.” As in tuberculosis, so in bronchiectasis, association with other pulmonary lesions increased the incidence of right ventricular hypertrophy to over 36 per cent (Fig. 4).

In the entire group of patients with bronchiectasis, 16.2 per cent showed definite congestive failure and 7.4 per cent questionable failure. In the 68 patients with bronchiectasis “alone,” there were 4.4 per cent with definite congestive failure and 3 per cent with questionable failure, totaling 7.4 per cent.

Emphysema.—There were 129 cases (0.7 per cent) of moderate or marked emphysema, and 30.2 per cent of these patients presented right ventricular hypertrophy.

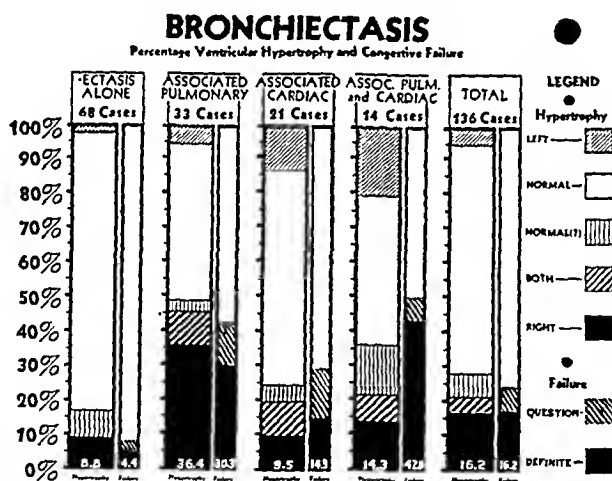


Fig. 4.

Of 45 patients with emphysema “alone,” 28.9 per cent had right ventricular hypertrophy, which is nearly the same percentage as in the total group of emphysema cases. If cases in which both ventricles were hypertrophied are also included, the right ventricle was hypertrophied in 47 per cent of the patients in the total emphysema group, as compared with 40 per cent in those with emphysema “alone” (Fig. 5). These figures are in general agreement with the conclusions of Kountz, Alexander, and Prinzmetal,⁴ who separated and weighed the right and left ventricles of the hearts of 17 patients with marked emphysema. They concluded that the heart is affected in the majority of cases of emphysema.

In the total group of patients with emphysema, 38.8 per cent showed definite congestive failure, and 20.1 per cent questionable failure, total-

ing 58.9 per cent. Of the 45 patients classed as having emphysema "alone," definite congestive failure occurred in 22.3 per cent and questionable failure in 15.6 per cent, totaling 37.9 per cent.

Asthma.—We did not list the cases of asthma separately. We agree with Lamson,⁵ and others, that asthma is a syndrome which may be associated with heart disease, or various pulmonary diseases, or may be due to allergy. Most of the patients with asthma due to allergy, in our series, also had emphysema. In our 45 cases of emphysema "alone," over 50 per cent of the patients were known to have had asthmatic attacks. We also included in this group 6 patients with asthma whose lungs showed slight emphysema. These had approximately the same percentage of cardiac findings as in the rest of the cases of emphysema "alone."

Pneumoconiosis.—In the 18,000 records reviewed, we found 97 cases (0.5 per cent) of pneumoconiosis. We included as pneumoconiosis cases of silicosis, anthracosis with moderate or marked fibrosis, and also fibrosis of unknown etiology, provided the silica content of the wet lung tissue was more than 2.5 mg. per cent.^{6*} Fibrosis in anthracosis is generally considered to be due to accompanying silicosis.⁷

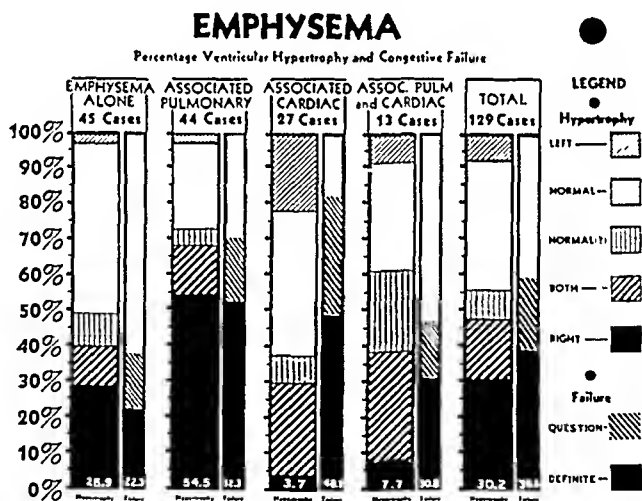


Fig. 5.

In the total group of 97 patients with pneumoconiosis, right ventricular hypertrophy occurred in 43.3 per cent. If instances of hypertrophy of both ventricles are included, the right ventricle was hypertrophied in 58.8 per cent. Of the 24 patients with pneumoconiosis "alone," 54.2 per cent showed right ventricular hypertrophy. If those with hypertrophy of both ventricles are included, 66.7 per cent showed right ventricular hypertrophy. This figure is higher than for the total group of pneumoconiosis. This is due possibly to earlier deaths of patients who had tuberculosis, or cardiac disease other than cor pulmonale (Fig. 6).

*The microdeterminations were kindly done by Albert L. Chaney, Ph.D., chemist at the Los Angeles County Hospital.

Definite congestive failure was present in 51.6 per cent of the total group of 97 patients, and questionable failure in 11.4 per cent, making a total of 63 per cent. Of the 24 patients with pneumoconiosis "alone," 50 per cent showed definite congestive failure and 16.7 per cent questionable failure, totaling 66.7 per cent.

Though Dyson,⁸ Jaffe,⁹ and others^{10, 11} have discussed the cardiac changes in pneumoconiosis, the importance of this complication is not generally appreciated. In our series, contrary to the usual impression, the number of patients who died with congestive failure was even greater than the number of those who had an associated tuberculosis. It has been thought⁷ that patients with anthracosilicosis are less susceptible to tuberculosis than patients with pure silicosis. The presence of anthracosilicosis in some of the patients may explain the lower incidence of tuberculosis in our group. Sweany, Porsche, and Douglass⁷ state that these cardiac changes occur in advanced cases. In another study,¹² we were able to confirm this opinion. We believe that congestive failure, when due to cor pulmonale, is usually a terminal event.

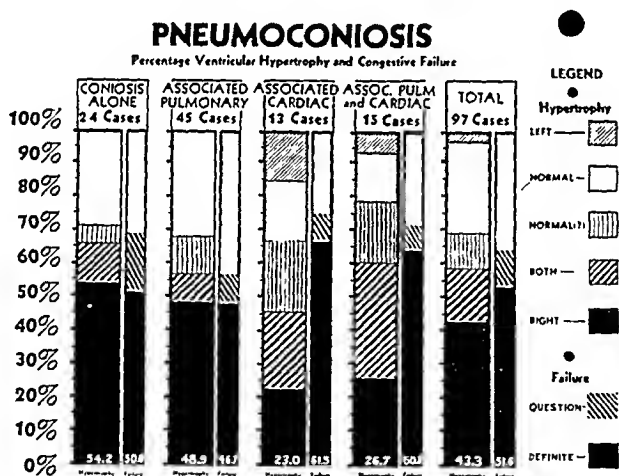


Fig. 6.

Nonspecific Pulmonary Fibrosis.—In 14 cases the fibrosis apparently was not due to tuberculosis or pneumoconiosis. Some were listed as "interstitial pneumonitis, etiology undetermined." Some, from the description in the record, might have been pneumoconiosis, but we were unable to verify this impression. These 14 patients showed approximately the same cardiac findings as did those with pneumoconiosis; 64 per cent had right ventricular hypertrophy, and 42 per cent developed definite congestive failure.

Spinal Deformities.—Only 5 cases of scoliosis or kyphoscoliosis were found in the autopsy index. These were of severe degree, and no doubt many other cases of slight or moderate deformity had gone unindexed. Of these 5 patients, definite hypertrophy of the right ventricle was

found in 3; in one there was dilatation without hypertrophy, and in one no anatomic change. This group is too small to be of statistical value, but the findings agree with those of Bachmann.¹³ From a clinical study, Edeiken¹⁴ concluded that spinal deformities, especially scoliosis and kyphoscoliosis, have a profound effect upon the lungs, and that the effect upon the heart is probably secondary to the pulmonary changes in most instances. Our 5 patients all had such pulmonary lesions.

Pulmonary Arteriolar Sclerosis.—The lungs in the group of 26 patients listed as having “pulmonary arteriolar sclerosis” had been carefully sectioned and the arterioles studied because of the marked degree of right ventricular hypertrophy which was found at autopsy. A high incidence of right ventricular hypertrophy and congestive failure in this group was therefore to be expected. Nearly all the hearts showed marked hypertrophy of the right or of both ventricles. Definite congestive failure was present in 61.5 per cent of this entire group and in 57.1 per cent of the 7 patients with pulmonary arteriolar sclerosis “alone.”

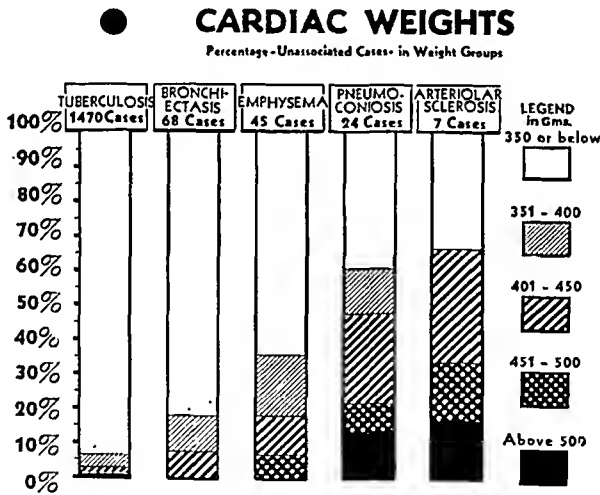


Fig. 7.

Weight of Hearts.—The percentage of hearts with increased weights was found to parallel closely the percentage of thickened right ventricular walls in the various pulmonary disease groups. The tuberculosis group showed the largest percentage of hearts weighing 350 gm. or less. Normal heart weights were next most frequent in bronchiectasis, then came emphysema, while the pneumoconiosis and pulmonary arteriolar sclerosis groups showed the lowest percentage of hearts weighing 350 gm. or less. On the other hand, pneumoconiosis was the only group, with the exception of pulmonary arteriolar sclerosis (a specifically selected group), in which there were hearts weighing over 500 gm. without associated cardiac lesions. Similarly, emphysema and pneumoconiosis were the only groups in which hearts weighing over 450 gm. were found. These facts are shown graphically in Fig. 7.

SUMMARY AND CONCLUSIONS

1. The protocols of all chronic pulmonary lesions indexed in 18,000 consecutive autopsies were studied to ascertain the incidence of cor pulmonale in the more common pulmonary diseases, as evidenced by right ventricular hypertrophy and congestive cardiac failure. These cases were grouped according to their association with other pulmonary or cardiac lesions.

2. Chronic pulmonary disease is an important cause of cor pulmonale. The various pulmonary lesions varied greatly in their effect upon the heart. For comparative analysis, conclusions are drawn only from the group of cases in which there was no other pulmonary or cardiac disease (cases "alone") (Fig. 8).

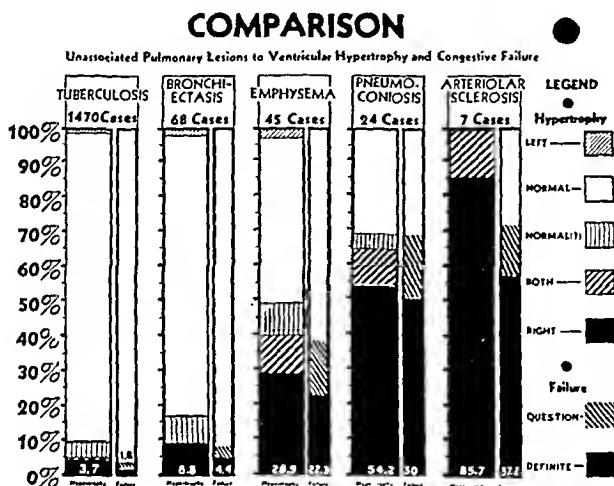


Fig. 8.

3. Pneumoconiosis showed the highest percentage incidence of cor pulmonale. Right ventricular hypertrophy occurred in 54.2 per cent, and definite congestive failure in 50 per cent, of 24 patients without other pulmonary or cardiac disease. The number of patients with pneumoconiosis who died with definite congestive failure was even greater than the number of those who had an associated tuberculosis.

4. Emphysema ranked second in percentage incidence. Right ventricular hypertrophy occurred in 28.9 per cent, and definite congestive failure in 22.3 per cent, of 45 uncomplicated cases.

6. The hearts of patients with pulmonary tuberculosis showed right ventricular hypertrophy in but 3.7 per cent, and definite congestive failure in 1.8 per cent, of 1,470 cases. The tuberculosis group had the lowest percentage of right ventricular hypertrophy of all chronic pulmonary disease groups, except chronic bronchitis. Nevertheless, due to the high incidence of tuberculosis, right ventricular hypertrophy was seen more frequently at autopsy in patients with tuberculosis than with any other pulmonary disease.

7. Cardiac hypertrophy, as evidenced by increased heart weights, was found to parallel closely the percentage of thickened right ventricular walls in the various chronic pulmonary disease groups.

REFERENCES

1. Herrmann, G. R., and Wilson, F. N.: Ventricular Hypertrophy, Comparison of Electrocardiographic and Post-Mortem Observations, *Heart* 9: 91, 1922.
2. Thompson, William P., and White, Paul D.: The Commonest Cause of Hypertrophy of the Right Ventricle—Left Ventricular Strain and Failure, *AM. HEART J.* 12: 641, 1936.
3. Nemet, Geza, and Rosenblatt, Milton B.: Cardiac Failure Secondary to Chronic Pulmonary Tuberculosis, *Am. Rev. Tuberc.* 35: 713, 1937.
4. Kountz, W. B., Alexander, H. L., and Prinzmetal, M.: The Heart in Emphysema, *AM. HEART J.* 11: 163, 1936.
5. Lamson, Robert W.: Asthma—A Syndrome, Not a Clinical Entity, *Journal-Lancet* 57: 90, 1937.
6. DeEds, F., and Eddy, C. W.: Microdetermination of Silicon, *J. Biol. Chem.* 114: 667, 1936.
7. Sweany, Henry C., Porsche, Julius D., and Douglass, Jesse R.: Chemical and Pathological Study of Pneumoconiosis, *Arch. Path.* 22: 593, 1936.
8. Dyson, J. M.: Pulmonary Heart Disease in Pneumoconiosis, *AM. HEART J.* 9: 764, 1934.
9. Jaffe, R. H.: The Pathology of Pneumoconiosis, *Illinois M. J.* 66: 431, 1934.
10. McCann, William S.: From Russell L. Cecil's *A Textbook of Medicine*, Ed. 4, p. 883, Philadelphia, 1937, W. B. Saunders Company.
11. White, Paul D.: *Heart Disease*, Ed. 2, p. 336, New York, 1937, The Macmillan Company.
12. Coggin, Charles B., Griggs, Donald E., and Stilson, Walter L.: The Heart in Pneumoconiosis, *AM. HEART J.* 16: 411, 1938.
13. Bachmann, M.: Die Veränderungen an den inneren Organen bei hochgradigen Skoliosen und Kyphoskoliosen, *Bibliotheca Med.*, Abt. D. Heft. 4, Stuttgart, 1899. (Quoted by Edeiken.)
14. Edeiken, Joseph: The Effect of Spinal Deformities on the Heart, *Am. J. M. Sc.* 186: 99, 1933.

PHARMACOLOGY OF CHEYNE-STOKES RESPIRATION*

M. H. NATHANSON, M.D., AND J. P. FITZGIBBON, M.D.
LOS ANGELES, CALIF.

CYCLIC respiration with periods of apnea and hyperpnea is most frequently encountered in association with cardiac disease, cerebral disturbances, spontaneous or traumatic, and with uremia. In cerebral accidents and uremia the respiratory disturbance is usually overshadowed by the other manifestations of the disease and ordinarily does not require consideration in therapy. In heart disease the cyclic breathing frequently results in great subjective distress, and, by interfering with the patient's rest and sleep, becomes a definite factor in preventing improvement of the cardiac state. In the more extreme cases the periodic breathing is continuous, and the patient is constantly disturbed by the repeated cycles of deep breathing. Continuous sleep is impossible, the exhausted patient dozing for a few seconds, only to be aroused by the deep breathing which follows the period of apnea. Under these conditions a patient may go for days without obtaining more than one minute's continuous sleep. Frequently, periodic breathing is the mechanism of nocturnal attacks of orthopnea and restlessness, preventing any prolonged period of continuous sleep.

Vogl, in 1927, first used theophylline with ethylenediamine (aminophyllin) in the treatment of cyclic breathing and reported the results of five years of observation in 1932.¹

He concluded that periodic breathing and the associated subjective distress could be consistently abolished by intravenous administration of the drug. Others^{2a, 2b} have confirmed the observations of Vogl. Although this action of aminophyllin is quite generally known, it is rather surprising that there are but few reports on the subject in the literature. The reports mentioned^{2a, 2b} include studies of a small group of cases and are devoted mainly to speculation as to the possible mode of action of the drug. In this country this action of aminophyllin was mentioned by Smith and his associates,³ in 1935. Other studies by the Iowa group are those of Paul, Greene, and Feller,⁴ who showed that aminophyllin reduced the intravenous and intrathecal pressures in patients with Cheyne-Stokes breathing. The largest series of patients studied is that of Greene and Heeren,⁵ in 1936, who carried out a systematic investigation which was controlled by graphic respiratory records. They studied a number of substances and found that complete abolition of the respiratory arrhythmia was observed only after the administration of amino-

*Read before the American Heart Association, San Francisco, Calif., June 10, 1938.

From the Department of Medicine, University of Southern California, Medical Service, Los Angeles County General Hospital.

Received for publication Nov. 15, 1938.

phyllin. In the report of the Council on Pharmacy and Chemistry of the American Medical Association, in 1930, on theobromine and theophylline compounds, no mention was made of any action on the respiration.⁶ In a more recent report, in 1937, the statement made in discussing the action of aminophyllin on Cheyne-Stokes respiration is that "reports on such an action are for the most part unverified and the observations are uncontrolled."⁷ In the discussion of theophylline in two standard textbooks of pharmacology, Sollmann, 1937,⁸ and Bastedo, 1938,⁹ no mention is made of this action of theophylline. In 1937, Marais and McMichael¹⁰ carried out a study on theophylline in Cheyne-Stokes breathing, concluding that the effective substance in aminophyllin is ethylenediamine and that theophylline itself is inactive.

The purpose of the present investigation was, first, to study in detail the action of aminophyllin and other drugs in Cheyne-Stokes breathing, and second, to repeat the studies of Marais and McMichael in order to establish more definitely what the active substance is. In the first series of cases graphic records were not made. In this group 0.24 gm. of the drug was administered intravenously in twelve patients, with restoration of normal breathing in eight. For comparison, coramine in 2 c.c. doses was administered to three patients who responded to aminophyllin. Coramine was without effect on the respiratory disturbance. In the second group, consisting of twenty-six patients, graphic respiratory records were made. Each record shows a control period, a period of drug administration, and a variable period following the administration of the drug. Of the twenty-six patients studied, twenty were suffering from varying degrees of cardiac decompensation associated with hypertension or coronary disease. Uremia was present in three instances and in three patients the cyclic breathing followed a cerebral accident. Forty-four observations were made, and the following drugs used: theophylline with ethylenediamine in eighteen patients, theophylline monoethanolamine in seven, ethylenediamine in five, benzedrine in three, caffeine sodiobenzoate in three, theophylline isopropanolamine in two, theophylline methylglucamine in two, and theophylline sodium acetate in four. Aminophyllin was administered in this series in doses of .48 gm. dissolved in 20 c.c. of water. This was injected intravenously, taking 3 to 5 minutes for the injection. Of the eighteen patients receiving aminophyllin, normal breathing was restored in sixteen. The drug failed in two instances. In one the respiratory disturbance was in a patient with coronary occlusion who died within a few hours. The second failure was in a case of massive cerebellar hemorrhage which caused death within a few hours. These results compare well with those of Greene and Heeren,⁵ who were able to restore normal breathing in forty-five out of forty-nine trials. The effect of the drug was immediate in all instances, rhythmic breathing being established before the injection was completed (Figs. 1 and 2). During or shortly after the com-

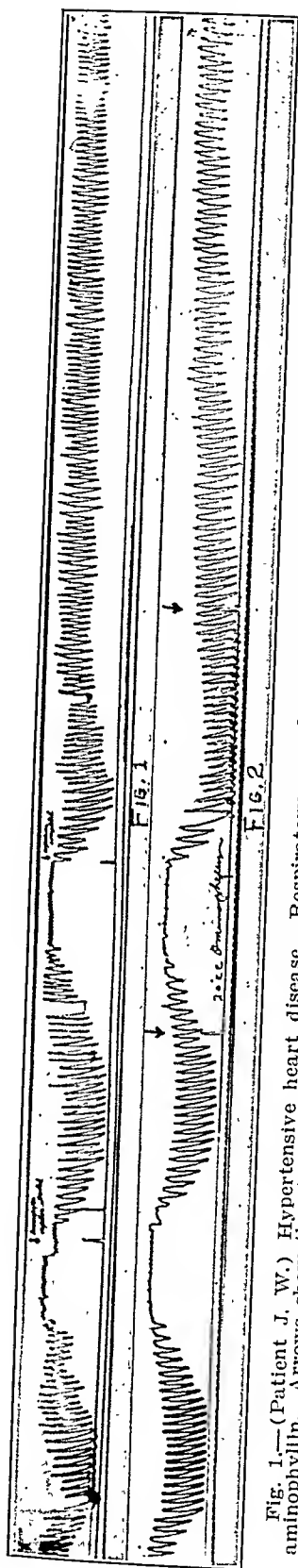


Fig. 1.—(Patient J. W.) Hypertensive heart disease. Respiratory record, showing the effect of an intravenous injection of 0.48 gm. of aminophyllin. Arrows show the start and finish of the injection. Note the complete disappearance of cyclic breathing. In all records, expiration is represented by the upstroke and inspiration by the downstroke. Note that with the disappearance of cyclic breathing the expiratory level is that of the apnea level.

Fig. 2.—(Patient A. K.) Hypertensive heart disease. Respiratory record, showing the effect of .48 gm. of aminophyllin intravenously. Arrows indicate the start and end of the injection.

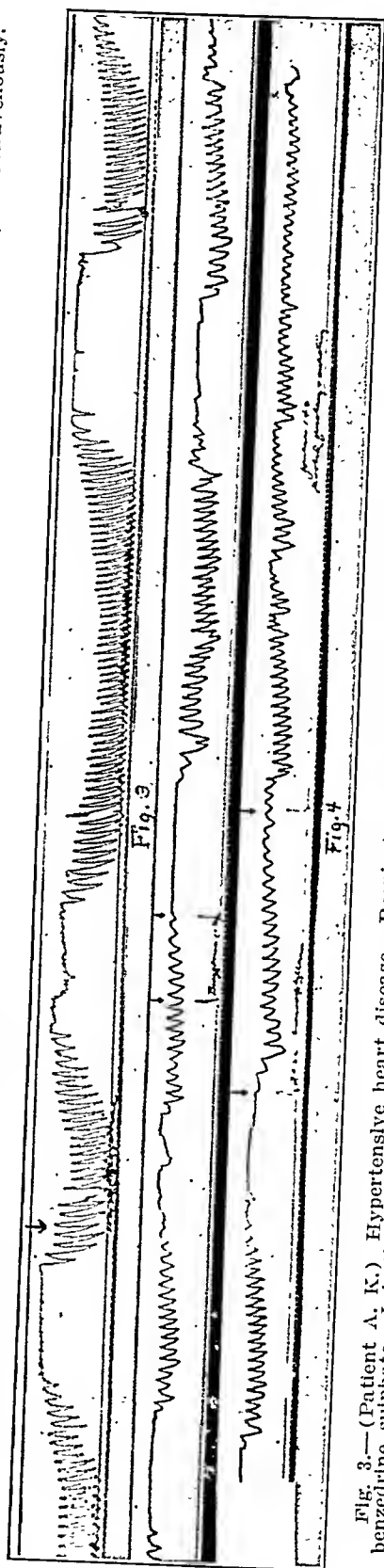


Fig. 3.—(Patient A. K.) Hypertensive heart disease. Respiratory record, showing the effect of the intravenous injection of 10 mg. of benzedrine sulphate. Injection started at arrow. Note the prolongation of the respiratory phase, without effect on the cyclic breathing.

Fig. 4.—(Patient M. D.) Hypertension. Upper strip shows the continuance of cyclic breathing after the intravenous administration of 10 mg. of benzedrine sulphate. Lower strip shows the disappearance of cyclic breathing after the intravenous administration of 10 mg. of aminophyllin intravenously. Arrows indicate the beginning and end of the injection.

pletion of the injection there was usually a period of increased depth of breathing which was quickly followed by a reduction of the amplitude of the respirations. The duration of the effect varied from twenty minutes to a permanent restoration of normal breathing after a single injection. Most frequently the effect lasted from six to eight hours. In cardiac failure, the duration of the normal respiration appeared to depend on the severity of the failure, with a shorter duration in the more severe cases. However, even in patients with marked failure, the effect usually lasted for many hours.

Benzedrine is an adrenaline-like substance which has an intense stimulating action on the central nervous system.¹¹ There is no general agreement as to the underlying mechanism of Cheyne-Stokes breathing, but it has been frequently suggested that periodic respiration results from a depressed respiratory center. For this reason it was thought that the effect of a drug stimulating the central nervous system might be of interest. In three patients, 10 mg. of benzedrine sulphate were injected intravenously, and in no instance was the cyclic breathing abolished; in each case the injection was followed by one or two cycles of prolongation of the hyperpneic phase (Figs. 3 and 4). In each of the three patients failing to respond to benzedrine, aminophyllin abolished the cyclic breathing. Caffeine sodium benzoate in doses of 0.75 gm. was administered to three patients. In one case this was followed by normal breathing for 20 minutes. In the same patient aminophyllin restored normal respiration for several hours (Fig. 5). In two patients the drug had no effect on the respiratory disturbance, while aminophyllin showed its characteristic action.

Aminophyllin is theophylline with ethylenediamine, consisting of approximately 75 per cent theophylline and 25 per cent ethylenediamine. The drug was first introduced as a diuretic, in 1908, by Dessauer,¹² as a result of the search for a water-soluble theophylline compound for parenteral administration. Theophylline itself is relatively insoluble, and the double salt of theophylline with sodium acetate, soluble theocin, is soluble only in 25 parts of water. Theophylline with ethylenediamine is freely soluble in water, nonirritating, and easily forms a 40 per cent solution. At the outset it was considered that ethylenediamine was pharmacologically inert and played no part in the action of the theophylline compound. However, Vogl¹ reported a case in which cyclic breathing was abolished by ethylenediamine itself. Guggenheimer^{2a} concluded that ethylenediamine increased the activity of theophylline. Grüter^{2b} claimed that the combination of theophylline with ethylenediamine resulted in a more active diuretic substance than theophylline with other aliphatic amines. He also felt that ethylenediamine contributed to the coronary dilating action of aminophyllin. Marais and McMichael,¹⁰ in 1937, came to the conclusion that the effect of aminophyllin in Cheyne-

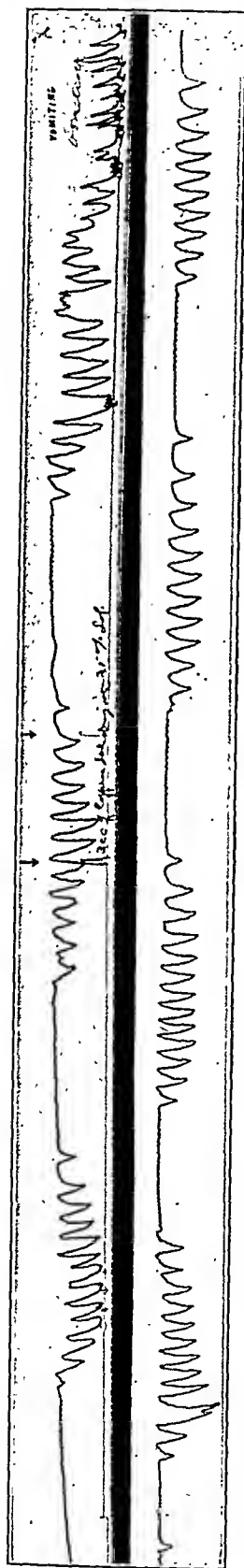


Fig. 5.—(Patient M. D.) Hypertension. This is a continuous record showing the ineffectiveness of .75 gm. of caffeine sodiobenzoate intravenously. Arrows indicate beginning and end of injection. Fig. 4, lower strip, shows this patient's response to aminophyllin.

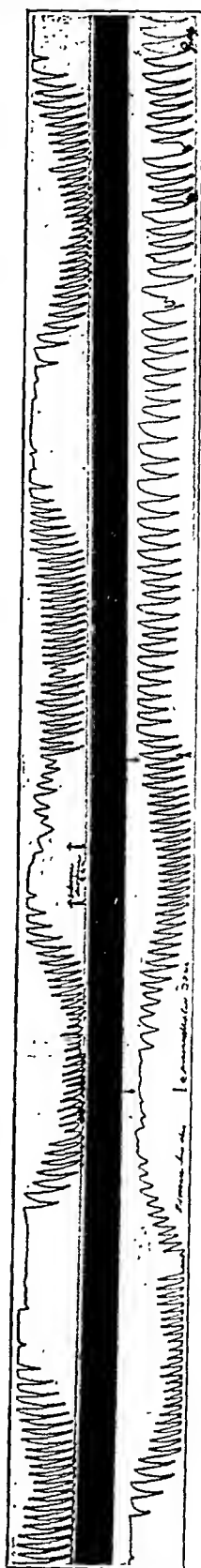


Fig. 6.—(Patient T. A.) Coronary thrombosis. Upper strip shows the continuance of cyclic breathing after the intravenous injection of 200 mg. of ethylenediamine. Lower strip shows the disappearance of cyclic breathing after .48 gm. of aminophyllin. Arrows indicate the start and end of the injection.

Stokes respiration was due mainly to its ethylenediamine component, and that theophylline itself was inactive. It seemed important to repeat this study, for if the amine were the active substance, a wide field for further pharmacologic study of cyclic breathing would be opened, as there is an almost unlimited number of related substances, many physiologically more active than ethylenediamine. In reviewing the report of Marais and McMichael it did not seem that their results were entirely convincing. The ethylenediamine was used in only three patients with Cheyne-Stokes breathing. The effect of the drug was of very short duration and was not at all comparable to the action of aminophyllin. In one case the ethylenediamine abolished the apneic phases, but periodic cyclic breathing still persisted. A subsequent injection of theophylline completed the restoration of normal rhythm. In the same patient, subsequently, only a transient abolition of periodic breathing was obtained with ethylenediamine, while aminophyllin abolished the cyclic breathing for two hours. In a third patient ethylenediamine restored normal respiratory rhythm. This was followed by theophylline, but the duration of the effect of both compounds was only fifteen minutes. At this time 0.48 gm. aminophyllin was injected, and the breathing was still regular twenty-two hours after the injection.

In the present study ethylenediamine was administered intravenously in 200 mg. doses to five patients. In one instance there was a very brief modification of the cyclic breathing; in the remaining four the drug was entirely without effect. Aminophyllin was then injected and was followed in each instance by its characteristic effect (Fig. 6). The effective dose of aminophyllin, 0.48 gm., contains approximately 125 mg. of ethylenediamine, so that the dose of ethylenediamine used was in excess of the amount present in an effective dose of aminophyllin. With the exception of Marais and McMichael,¹⁰ who included some observations on the effect of theophylline sodium acetate, all observers have confined their investigations in Cheyne-Stokes respiration to theophylline with ethylenediamine. In order to study further the importance of the ethylenediamine fraction, the action of theophylline in combination with other amines was investigated. Theophylline with monoethanolamine was administered to seven patients with cessation of cyclic breathing in each instance. The onset and duration of the effect were similar to what was observed with aminophyllin (Fig. 7). Theophylline isopropanolamine and theophylline methylglucamine were administered to two patients, and the injection was followed by restoration of normal breathing in each case (Figs. 8 and 9). The question then arose whether the amine was at all necessary for this action, and therefore in four patients theophylline sodium acetate in doses of 0.66 gm. was administered, and this was also followed by the abolition of the cyclic breathing (Fig. 10). It should be

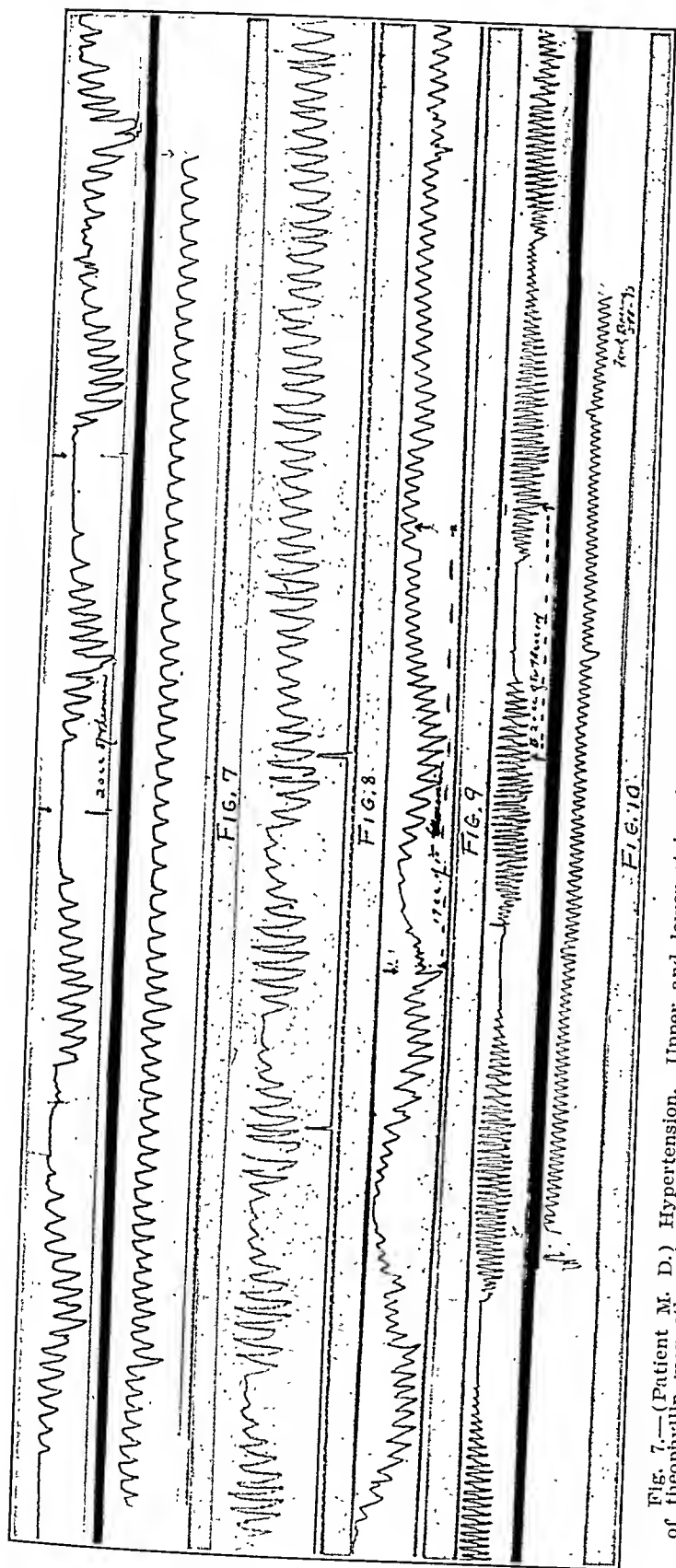


Fig. 7.—(Patient M. D.) Hypertension. Upper and lower strips form a continuous respiratory record, showing the effect of .48 gm. of theophyllin monoethanolamine. Note the disappearance of cyclic breathing. Figs. 4 and 5 show the ineffectiveness of benzedrine and intravenously. Note the disappearance of cyclic breathing. Respiratory record, showing the effect of .48 gm. of theophyllin isopropanolamine indicate beginning and end of injection.

Fig. 8.—(Patient J. S.) Hypertensive heart disease. Respiratory record, showing the effect of .4 gm. of theophyllin methylglucamine. Arrows theophyllin sodium acetate intravenously. Arrows indicate the time of injection. Note the disappearance of cyclic breathing.

Fig. 9.—(Patient J. A.) Cerebral thrombosis. Respiratory record, showing the effect of .4 gm. of theophyllin methylglucamine. Arrows theophyllin sodium acetate intravenously. Arrows indicate the time of injection. Note the disappearance of cyclic breathing.

Fig. 10.—(Patient F. B.) Hypertension. Upper and lower strips form a continuous respiratory record showing the effect of .66 gm. of theophyllin monoethanolamine. Note the disappearance of cyclic breathing.

mentioned that in each instance in the above studies the amount of theophylline administered was approximately the same and was equivalent to the amount contained in 0.48 gm. of aminophyllin. It is felt that these observations indicate definitely that the ethylenediamine is of little importance in the action of the theophylline compounds and that the desired action may be obtained by theophylline in any combination.

MODE OF ACTION

The exact mechanism of the action of the theophylline compounds in Cheyne-Stokes respiration is not clear. This is not surprising, for there is no generally accepted explanation of the mechanism underlying cyclic breathing. There are several theories concerning the mode of action of the drug, but each is open to some objection. It has been suggested by Vogl¹ that the drug produces normal breathing by stimulating a depressed respiratory center. This concept is open to the objection that carbon dioxide, which is a powerful respiratory stimulant, does not reproduce the effect of theophylline in Cheyne-Stokes breathing.⁵ Furthermore, such drugs as coramine and lobeline, which definitely stimulate an experimentally depressed respiratory center, are not effective in cyclic breathing. Greppi¹³ demonstrated a rapid drop in spinal fluid pressure after the intravenous administration of aminophyllin in thirteen of sixteen individuals. He believed that this was most probably the result of the action of aminophyllin on the cerebral circulation. Paul, Greene, and Feller⁴ found that aminophyllin reduced the intravenous and intrathecal pressures and suggested from these observations that cyclic breathing is abolished by an improvement in the cerebral circulation. Reduction in the cerebrospinal fluid pressure alone is apparently ineffective, for Greene and Heeren⁵ found that the administration of 50 per cent glucose had no effect. Guggenheimer^{2a} explained the action of aminophyllin on the basis of an increased cerebral circulation resulting from cerebral vasodilatation and improved cardiac action. He presents no experimental evidence to support this theory. It is evident that the cardiac effect of theophylline may be unimportant, because the drug is effective in periodic breathing unassociated with myocardial disease. The action of theophylline on the cerebral blood vessels has not been studied, but the related substance, caffeine, does produce cerebral vasodilatation.¹⁴ It is quite clear from the present studies that the effect of the drug is not confined to the respiratory center. When theophylline compounds are administered to patients who are in a comatose state, there is a distinct tendency toward return of consciousness. This action is often very striking and suggests that the drug has a widespread effect on the central nervous system such as may be brought about by a general increase in cerebral blood flow. In this connection, it is interesting that benzedrine, which

apparently acts directly on the central nervous system in doses which have no circulatory effect, is without influence in cyclic breathing.

It must be concluded that the exact mode of action of theophyllin on Cheyne-Stokes breathing is not clear. A direct action on the respiratory center is extremely unlikely. The demonstration by Greppi¹³ and by Paul and his associates⁴ that a reduction in intrathecal pressure is produced by aminophyllin suggests that the drug acts on the cerebral circulation. It would seem that further progress may follow more direct studies on the action of the drug on the cerebral circulation.

PRACTICAL APPLICATION

One might question the practical value of therapy for Cheyne-Stokes respiration. In fact, in a recent volume by Fishberg,¹⁵ the author states that "if one could abolish Cheyne-Stokes breathing, it is hardly of aid to the patient." This is entirely true in many instances when the respiratory disturbance is a terminal event. However, cyclic breathing with its attendant subjective distress may occur relatively early in the course of heart disease and, in some instances, the restoration of normal breathing gives not only subjective relief, but also by permitting the necessary rest is an aid in relieving cardiac failure. A dose of 0.24 gm. should be tried and, if this fails or if the duration of normal breathing is short, the larger dose of 0.48 gm. should be used. Of the thirty-three injections of the larger dose, unpleasant reactions followed in only a small number. These consisted of tachycardia, flushing of the face, sweating, and nausea.

The administration should be repeated when the cyclic breathing returns; usually not more than two or three doses a day are necessary.

In a small group of patients suffering from nocturnal respiratory distress, special enteric-coated tablets of a theophylline compound were administered by mouth. The dose was 0.6 gm. to 0.8 gm. in divided doses, given late in the day, usually 0.2 gm. doses at 6:00, 7:00, and 8:00 P.M. This was followed by good results in promoting restful sleep, making it possible to discontinue the use of sedatives.

CONCLUSIONS

Theophylline with ethylenediamine (aminophyllin) is a most effective drug in abolishing Cheyne-Stokes respiration.

The onset of the action is immediate, and the duration in the usual case is many hours, so that a dose of 0.48 gm. two or three times a day is sufficient to maintain rhythmic breathing.

The effective substance in aminophyllin is theophylline; ethylenediamine itself is ineffective; theophylline with other combinations shows its characteristic effect in Cheyne-Stokes breathing.

The following pharmaceutic houses gave generous supplies of their products: G. D. Searle and Company, Inc., theophylline ethylenediamine; Eli Lilly and Company, theophylline monoethanolamine; Abbott Laboratories, theophylline methylglucamine; The National Drug Company, theophylline isopropanolamine; Smith, Kline, and French Laboratories, benzedrine sulphate.

REFERENCES

1. Vogl, A.: Erfahrungen über Euphyllin bei Cheyne-Stokes und anderen Formen zentralen Atemstörung, *Med. Klin.* 28: 9, 1932.
- 2a. Guggenheimer, H.: Über die Wirkungsweise des Euphyllins bei Cardio-vascularen Cheyne-Stokes und Asthma Cardiale, *Ztschr. f. Kreislaufforsch.* 25: 98, 1933.
- 2b. Grüter, R.: Ueber das Theophyllin-Aethylindiamin, *München. med. Wchnschr.* 83: 1091, 1936.
3. Smith, F. M., Rathe, H. W., and Paul, W. D.: Theophylline in Treatment of Disease of Coronary Arteries, *Arch. Int. Med.* 56: 1250, 1935.
4. Paul, W. D., Greene, J. A., and Feller, A. E.: Some Observations on the Mechanism of Cheyne-Stokes Respiration, *Am. J. Physiol.* 119: 383, 1937.
5. Greene, J. A., and Heeren, R. H.: Observations on Cheyne-Stokes Respiration: The Effect of Drugs and Mechanical Measures Which Produce Vasodilatation and Vasoconstriction, *Medical Papers dedicated to Henry A. Christian, 1936*, Waverly Press, Inc.
6. Council on Pharmacy and Chemistry: Therapeutic Claims for Theobromine and Theophylline Compounds, *J. A. M. A.* 94: 1306, 1930.
7. Council on Pharmacy and Chemistry: Limitations of Claims for Aminophyllin and Other Xanthine Derivatives, *J. A. M. A.* 108: 2203, 1937.
8. Sollmann, Torald: *A Manual of Pharmacology*, Philadelphia and London, 1937, W. B. Saunders Co.
9. Bastedo, W. A.: *Materia Medica, Pharmacology, Therapeutics and Prescription Writing*, Philadelphia and London, 1938, W. B. Saunders Co.
10. Marais, O. A. S., and McMichael, J.: Theophylline-Ethylenediamine in Cheyne-Stokes Respiration, *The Lancet* 233: 437, 1937.
11. Nathanson, M. H.: The Central Action of Beta-aminopropylbenzene (Benzedrine), *J. A. M. A.* 108: 528, 1937.
12. Dessauer, P.: Euphyllin, ein neues Diuretikum, *Therap. Monatsh.* 22: 401, 1908.
13. Greppi, E.: Ueber die Intrakraniell-drucksenkende Wirkung des Euphyllins, *Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch.*, pp. 316-318, 1934.
14. Finesinger, J. E.: Cerebral Circulation. Effect of Caffeine on Cerebral Vessels, *Arch. Neurol. and Psychiat.* 28: 1290, 1932.
15. Fishberg, A. M.: *Heart Failure*, Philadelphia, 1937, Lea and Febiger.

AN ELECTROCARDIOGRAPHIC STUDY OF TWINS

N. BOWMAN WISE, M.D., DURHAM, N. C., WILFRID J. COMEAU, M.D.,
AND PAUL D. WHITE, M.D., BOSTON, MASS.

THE many investigations which have been made of the resemblances and differences of identical twins do not include extensive electrocardiographic studies. We have been interested in this subject not only as a biological problem, but as an aspect of the study of the individuality of the electrocardiogram. In particular, our purpose in this investigation has been twofold: first, to discover the degree of similarity or difference manifest in the electrocardiograms of twins, and second, to determine whether the identity or nonidentity of a given pair of twins can be decided from careful comparison of their electrocardiograms.

Weitz¹ (1925), reporting an extensive study of identical twins, mentioned that electrocardiograms were obtained from the majority of twins studied by him. These electrocardiograms were said to be readily separable into their proper pairs by inspection alone, but no specific data were given regarding the records. Almeida² (1929) secured electrocardiograms from a pair of twins who came under his observation. These electrocardiograms coincided when superimposed, which fact Almeida considered as additional evidence of the identity of these twins. Parade³ (1935) reported an electrocardiographic study of ten pairs of identical twins. The records of five pairs of twins were closely alike; varying degrees of similarity or difference were found in the records of five other pairs.

The present study embraces thirty-two pairs of identical twins and eighteen pairs of nonidentical twins, a total of fifty pairs. The majority of these individuals were under 30 years of age. Careful histories were taken from forty-three of the fifty pairs of twins, to exclude possible etiological factors for heart disease; physical examination of the heart and lungs was made in this group. In order to bring out similarities or differences in the twins, notations were made of body build, height, weight, hair color, eye color, and left- or right-handedness. Inquiry was also made as to the frequency with which the twins had been confused. A brief evaluation was taken of resemblance or difference in personality make-up. The final impression as to identity or nonidentity of the twins was established on the basis of all the data collected regarding each pair of twins.

The age, sex, height, and weight of the majority of the twins studied were as follows (Table I), including fifty-eight of the sixty-four identical twins and twenty-one of the thirty-six nonidentical twins.

¹With the cooperation of Wellford C. Reed, William H. Gordon, and William Paul Thompson.

²From the Cardiac Clinic of the Massachusetts General Hospital, Boston.

Received for publication Nov. 11, 1938.

TABLE I
IDENTICAL TWINS

TWIN	AGE	SEX	HEIGHT (INCHES)	WEIGHT (POUNDS)
G.	47	F	66.7	145.0
H.			65.0	143.5
W.	25	M	69.0	153.0
J.			69.0	150.0
P.	21	F	61.5	125.5
H.			60.6	119.0
D.	27	F	66.8	148.0
E.			66.5	140.5
S.	34	M	70.2	155.3
G.			70.1	155.3
V.	22	F	64.0	120.5
G.			64.8	119.3
V.	21	M	70.5	156.0
J.			70.1	156.0
Dor.	21	F	63.5	106.0
Do.			63.5	111.0
Jo.	15	F	64.7	129.8
Je.			66.5	125.0
A.	21	M	64.5	135.3
M.			65.0	136.8
H.	21	F	65.0	113.0
G.			65.0	120.5
Ba.	21	F	62.0	123.0
Be.			61.0	119.0
T.	17	F	61.9	126.5
I.			62.2	119.0
H.	20	F	64.0	127.0
E.			64.5	129.0
A.	21	M	66.8	144.0
J.			69.0	148.3
L.	22	F	63.5	110.0
F.			62.1	109.0
W.	21	M	65.0	132.0
F.			65.7	140.8
M.	32	F	65.3	131.3
C.			64.8	148.5
A.	22	F	62.5	136.0
J.			63.0	139.8
N.	19	F	63.5	133.0
P.			63.5	127.0
E.	21	F	61.5	151.5
I.			62.0	109.0
Ca.	27	F	64.3	137.0
Ch.			63.5	123.0
D.	26	F	59.0	88.5
G.			59.0	91.0
D.	41	F	65.3	119.5
K.			65.3	123.0
F.	19	F	66.0	125.5
P.			66.0	130.0
A.	35	F	64.0	136.0
E.			65.0	141.0
G.	22	M	69.5	157.0
L.			69.5	157.0
V.	23	F	67.0	137.0
F.			67.0	134.5
W.	22	M	66.0	132.0
B.			66.0	130.3

TABLE II
NONIDENTICAL TWINS

TWIN	AGE	SEX	HEIGHT (INCHES)	WEIGHT (POUNDS)
M. }	22	F	67.5	131.0
M. }			69.5	147.0
R. }			62.5	130.0
V. }	22	M	63.5	120.0
Mi. }			43.5	45.5
Ma. }			44.5	45.0
H. }	21	M	65.8	124.3
A. }			63.7	128.7
A. }			59.9	179.8
V. }	21	F	59.9	132.5
Ru. }			64.6	118.8
Ro. }			61.4	101.2
H. }	21	F	64.5	112.0
G. }			63.0	118.5
C. }			72.0	158.0
J. }	23	M	70.8	194.0
V. }			65.3	151.0
E. }			65.3	142.0
M. }	21	F	69.0	136.0
J. }			69.5	141.0
F. }			67.5	136.0
S. }	21	M	69.0	135.0

All of the individuals in this series were considered to have normal hearts with the exception of one, who had evidence of mitral stenosis on physical examination, but had no cardiac symptoms. The electrocardiograms of two pairs of twins exhibited low T waves in the conventional leads. The electrocardiograms of another pair of twins (aged 21 years) showed inverted T waves in the preecordial leads. The remainder of the electrocardiograms of the twins were well within the usual normal limits.

In deciding the measure of similarity shown in the electrocardiograms of the twins studied, not only has the character of the deflections been considered, but also their amplitude. The electrocardiograms of both identical and nonidentical twins have been conveniently grouped as showing "close similarity," "some similarity," "no similarity." The absolute criteria for such designations have been established from comparison of the amplitudes of the deflections, especially of the QRS waves, in the conventional leads. Electrocardiograms classed as showing "close similarity" are those which exhibit differences in the amplitude of similarly shaped QRS deflections of not more than 3 mm. in any conventional lead. Those records classed as having "some similarity" show differences in the amplitudes of the QRS deflections greater than 3 mm., but not exceeding 5 mm., in any classical lead. All electrocardiograms of twins which show differences in the amplitudes of the QRS deflections greater than 5 mm. in any lead are considered to show "no similarity"; such records are almost always dissimilar in shape as well as in size. The differences in the amplitudes of the QRS deflec-

tions of the precordial leads are not comparable to those found in the conventional leads and are considered mainly due to variations in the position of the precordial electrodes. For this reason the criteria for classification of the electrocardiograms of the twins, as applied to the conventional leads, do not include the precordial leads. The P and T waves which vary in amplitude between narrow limits in the electrocardiograms of twins have been found to show only slight differences in any lead, making it unnecessary to consider these deflections in establishing criteria for the grouping of the records.

TABLE III
ELECTROCARDIOGRAMS

TYPE OF TWINS	NUMBER OF CASES	CLOSE SIMILARITY	SOME SIMILARITY	NO SIMILARITY
Identical	32	16 (50%)	8 (25%)	8 (25%)
Nonidentical	18	4 (22%)	5 (28%)	9 (50%)

ELECTROCARDIOGRAMS OF IDENTICAL TWINS

Of the thirty-two pairs of identical twins studied, the electrocardiograms of sixteen pairs of twins have been found to show "close similarity"; the records of eight other pairs show "no similarity." Among the electrocardiograms showing "close similarity," the first leads are most nearly identical, and the maximal differences are found in Lead III and in the precordial lead. The variations found in Lead III cannot be strictly correlated with the differences in weight of two to six pounds which existed between some individuals in this group, although differences in the height of the diaphragm may be of some importance.

The following are examples of the different degrees of similarity found to exist among the electrocardiograms of the identical twins.

ELECTROCARDIOGRAMS SHOWING CLOSE SIMILARITY

V. and J. C. are young men, 21 years of age, who are very much alike in appearance. It is of particular interest that both were refused army enlistment in 1936 because of albuminuria. Subsequently they were studied at the Boston City Hospital and found to have orthostatic albuminuria.⁴ It is said that while they were in the hospital they were constantly being confused, one for the other, by the ward staff. Their chief physical and electrocardiographic characteristics are given in Tables IV and V.

TABLE IV

TWIN	HAIR COLOR	EYE COLOR	HANDEDNESS	HEIGHT (INCHES)	WEIGHT (POUNDS)
V.	Sandy	Blue	Right	70.5	156
J.	Sandy	Blue	Right	70.1	156

TABLE V

LEAD	TWIN	P (MM.)	QRS (MM.)	T (MM.)
I	V.	+Trace	+2.0, -2.0	+1.5
	J.	+Trace	+3.0, -2.0	+2.0
II	V.	+1.5	-0.5, +11.0, -2.5	+2.0
	J.	+1.0+	-1.5, +11.0, -1.5	+2.5
III	V.	+1.0+	-2.0, +13.0, -2.0	+0.5
	J.	+1.0	-2.0, +10.5, -0.5	+0.5
IV	V.	+0.5	-6.0, +20.0	-4.5
	J.	+Trace	-5.0, +8.0	-5.0

ELECTROCARDIOGRAMS SHOWING SOME SIMILARITY

V. and F. D. are female graduate students, 23 years of age, who look alike and are often mistaken for each other. In temperament they are very much alike. Their chief physical and electrocardiographic characteristics are given in Tables VI and VII.

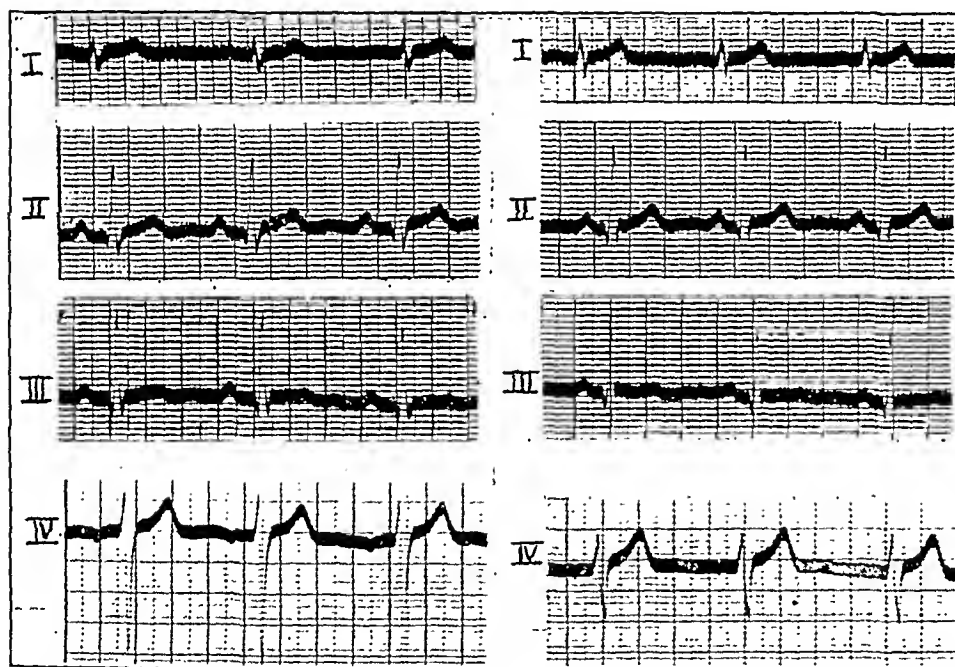


Fig. 1.—Electrocardiograms of identical twins V. and J. C., showing "close similarity" (left, V.; right, J.).

TABLE VI

TWIN	HAIR COLOR	EYE COLOR	HANDEDNESS	HEIGHT (INCHES)	WEIGHT (POUNDS)
V.	Blond	Hazel	Right	67.0	137.0
F.	Blond	Hazel	Right	67.0	134.5

ELECTROCARDIOGRAMS SHOWING NO SIMILARITY

G. and H. G. are female stenographers, 21 years of age, who are very much alike in appearance and are occasionally mistaken for each other. Their main physical and electrocardiographic characteristics are given in Tables VIII and IX.

TABLE VII

LEAD	TWIN	P (MM.)	QRS (MM.)	T (MM.)
I	V.	+0.5	+1.0, -1.0	+1.0
	F.	+0.5	+3.0, -1.0	+2.0
II	V.	+1.0	-1.0, +14.0	+1.5
	F.	+1.0	-1.0, +16.0	+1.5
III	V.	+ trace	-2.5, +16.0	diphasic trace
	F.	+ trace	-1.0, +11.0	-1.0
IV	V.	+1.0	+16.0, -2.0	+2.5
	F.	+1.5	-1.0, +18.0	+2.0

TABLE VIII

TWIN	HAIR COLOR	EYE COLOR	HANDEDNESS	HEIGHT (INCHES)	WEIGHT (POUNDS)
G.	Brown	Blue	Right	65.0	120.5
H.	Brown	Blue	Right	65.0	113.0

TABLE IX

LEAD	TWIN	P (MM.)	QRS (MM.)	T (MM.)
I	G.	+0.5	+2.5, -5.0	+1.0
	H.	+0.5	-0.5, +7.0, -2.0	+1.5
II	G.	+1.0	-trace, +11.0, -2.0	+1.5
	H.	+1.0	+10.0, -trace	+2.0
III	G.	+1.0	-1.0, +13.0	+1.0
	H.	+0.5	+3.0	+0.5
IV	G.	+1.0	+11.0, -6.0	+2.0
	H.	+0.5	+10.0, -4.0	+3.5

ELECTROCARDIOGRAMS OF THE NONIDENTICAL TWINS STUDIED

Of the eighteen pairs of nonidentical twins studied according to the criteria already mentioned, the electrocardiograms of four pairs have been found to show "close similarity." The records of five pairs showed "some similarity," and the records of nine pairs showed "no similarity." As was found in the electrocardiograms of the identical twins, the closest resemblance exists in the first leads, and the maximal differences are found in Lead III and in the precordial leads. Likewise, the P and T waves show only minimal differences regardless of the degree of similarity exhibited in the QRS waves. The following illustrate the findings in nonidentical twins.

ELECTROCARDIOGRAMS SHOWING CLOSE SIMILARITY

Ru. and Ro. D. are young women, 21 years of age, who differ markedly in body build and in general appearance, as is illustrated in Table X. Their personality make-ups are entirely different. Table XI gives their significant electrocardiographic findings.

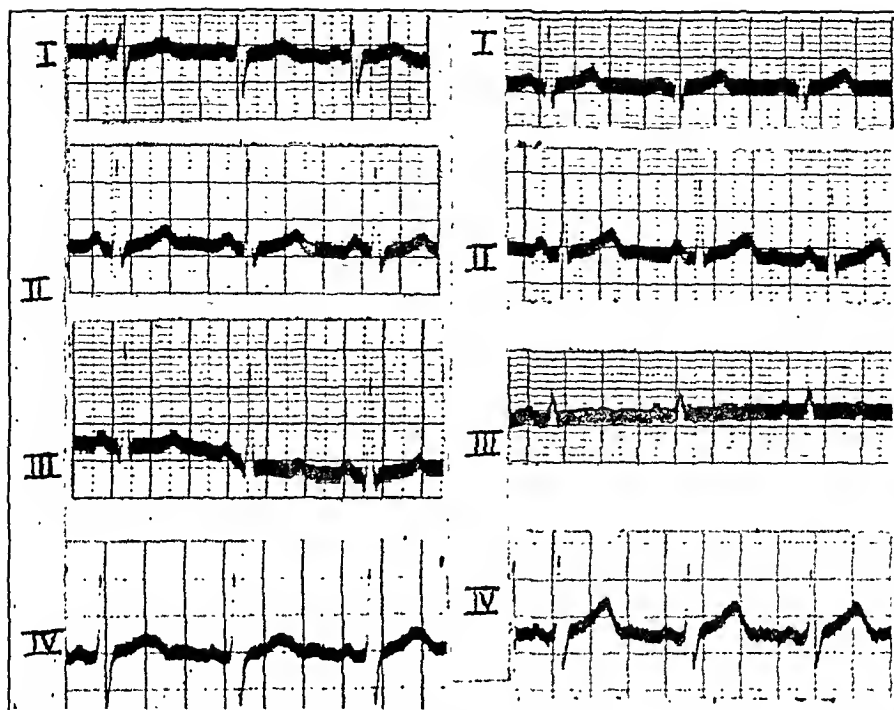


Fig. 2.—Electrocardiograms of identical twins G. and H. G., showing "no similarity" (left, G.; right, H.).

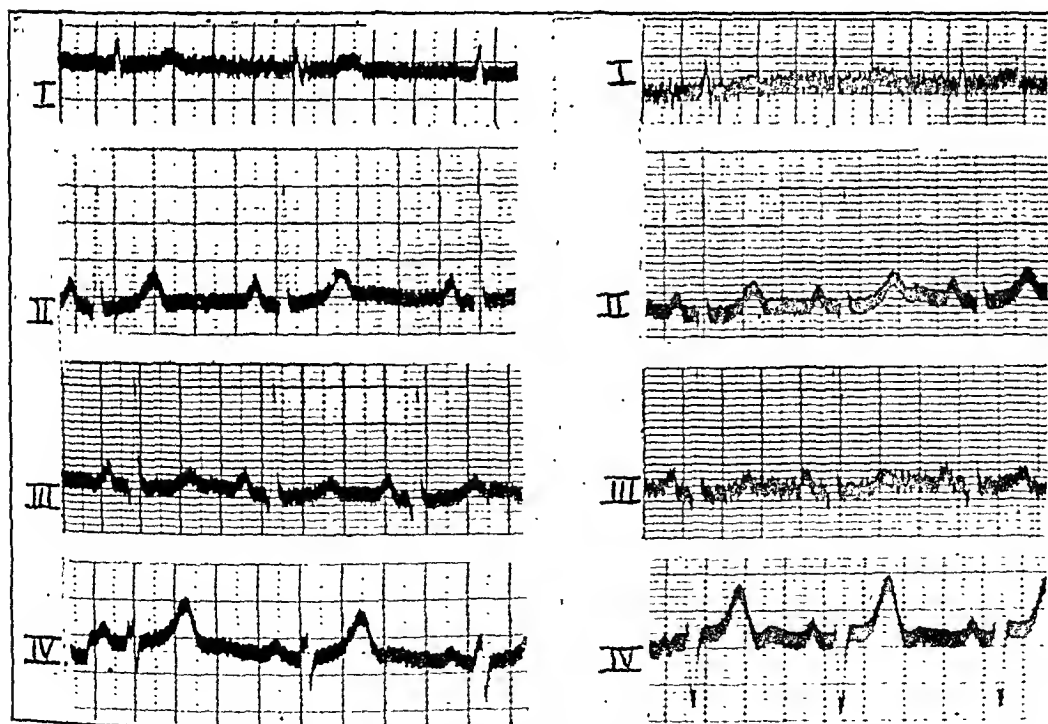


Fig. 3.—Electrocardiograms of nonidentical twins Ru. and Ro. D., showing "close similarity" (left, Ru.; right, Ro.).

TABLE X

TWIN	HAIR COLOR	EYE COLOR	HANDEDNESS	HEIGHT (INCHES)	WEIGHT (POUNDS)
Ru.	Brown	Blue green	Right	65	119
Ro.	Dark brown	Hazel	Right	61	99

TABLE XI

LEAD	TWIN	P (MM.)	QRS (MM.)	T (MM.)
I	Ru.	+ trace	+3.0	+1.0
	Ro.	+ trace	+3.5	+1.0
II	Ru.	+2.5	-trace, +16.0	+4.0
	Ro.	+2.0	-trace, +16.0	+3.5
III	Ru.	+2.0	-1.5, +15.0	+2.0
	Ro.	+2.0	-1.5, +16.0	+2.0
IV	Ru.	+1.5	+2.5, -4.0	+5.5
	Ro.	+2.0	+1.5, -9.0	+8.0

ELECTROCARDIOGRAMS SHOWING SOME SIMILARITY

F. and S. B. are male college students, 21 years of age, who do not resemble one another in appearance, and say that their personality make-ups are entirely unlike. Their physical and electrocardiographic characteristics, in brief, are given in Tables XII and XIII.

TABLE XII

TWIN	HAIR COLOR	EYE COLOR	HANDEDNESS	HEIGHT (INCHES)	WEIGHT (POUNDS)
F.	Brown	Green	Left	67.5	136
S.	Light brown	Blue-green	Right	69.0	135

TABLE XIII

LEAD	TWIN	P (MM.)	QRS (MM.)	T (MM.)
I	F.	+trace	+3.5, -1.0	+2.5
	S.	+0.5	+5.0, -1.5	+3.0
II	F.	+1.5	-trace, +14.0	+3.5
	S.	+1.0	-2.0, +18.0, -1.5	+4.0
III	F.	+1.0	+12.0	+1.5
	S.	+1.0	-2.0, +14.0	+1.5
IV	F.	+1.0	-trace, +18.0, -2.0	+5.0
	S.	+1.0	-2.0, +22.0, -2.0	+5.5

TABLE XIV

TWIN	HAIR COLOR	EYE COLOR	HANDEDNESS	HEIGHT (INCHES)	WEIGHT (POUNDS)
V.	Brown	Brown	Right	59.9	132.5
A.	Brown	Brown	Right	59.9	179.5

ELECTROCARDIOGRAMS SHOWING NO SIMILARITY

V. and A. C. are young women, aged 21 years, quite different in physique and in general appearance, and never mistaken for each other. Tables XIV and XV show their chief physical and electrocardiographic characteristics.

TABLE XV

LEAD	TWIN	P (MM.)	QRS (MM.)	T (MM.)
I	V.	+1.0	+5.0, -1.5	+2.0
	A.	+1.5	-trace, +11.0, -4.5	+3.0
II	V.	+1.0	-1.0, +14.0, -2.0	+3.0
	A.	+1.5	+11.0, -4.0	+3.0
III	V.	+0.5	-2.0, +12.0, -1.0	+0.5
	A.	-0.5	+1.0, -2.0, +3.0, -2.0	-0.5
IV	V.	+0.5	+10.0, -3.0	+1.5
	A.	+0.5	+14.0, -7.0	+2.0

DISCUSSION

The electrocardiograms of the twins studied have been found to show no such close degree of similarity as to permit exact superimposition of the records. The same degree of similarity or difference as may be found in the electrocardiograms of a pair of identical twins may also exist in the records of a pair of nonidentical twins, which fact precludes the determination of the identity or nonidentity of a given pair of twins from their electrocardiograms. The differences found in the electrocardiograms of identical twins cannot be strictly correlated with small differences in heights or weights, for differences of the same order are found in the electrocardiograms of identical twins of the same heights and weights. Furthermore, electrocardiograms of nonidentical twins differing markedly in body build may show close similarity. These findings are considered to illustrate the individuality of the electrocardiogram.

Our findings do indicate, however, that a close degree of similarity is more often to be found in the electrocardiograms of identical twins than in the electrocardiograms of nonidentical twins; the ratios in our series were 16:32 and 4:18, respectively.

During the course of this investigation a simultaneous orthodiagraphic and fluoroscopic study was made of the hearts of twins. The results are presented in a separate report.⁵

CONCLUSIONS

An electrocardiographic study has been made of thirty-two pairs of identical twins and eighteen pairs of nonidentical twins. Varying degrees of similarity or difference have been found in the electrocardiograms of all the twins studied. Close similarity or no similarity

may be found in the electrocardiograms of both identical and non-identical twins, for which reason the identity or nonidentity of a given pair of twins cannot be determined from study of their electrocardiograms alone, although identical twins did show a higher percentage of similar electrocardiograms than did nonidentical twins (ratio of 16 to 32, compared to that of 4 to 18). The lack of absolute correspondence of the electrocardiograms of identical twins of the same height and weight emphasizes the individuality of the electrocardiogram.

Addendum.—Since the completion of this report an extensive electrocardiographic study of 106 pairs of twins has been published by Parade and Lehmann (*Ztschr. f. menschl. Vererb.- u. Konstitutionslehre* 22: 96, 1938). Their results, using criteria similar to our own, are as follows:

ELECTROCARDIOGRAMS

TYPE OF TWINS	CLOSE SIMILARITY	SOME SIMILARITY	NO SIMILARITY
Identical	22 (41.5%)	25 (47.2%)	6 (11.3%)
Nonidentical	1 (1.9%)	19 (35.8%)	33 (62.3%)

These results, as well as others cited by Parade and Lehmann, are in general accord with our conclusions.

REFERENCES

1. Weitz, W.: Studien an eineigen Zwillingen, *Ztschr. f. klin. Med.* 101: 115, 1925.
2. Almeida, T.: Superposition de l'électrocardiogramme chez deux jumelles univitellines, *Compt. rend. Soc. de Biol.* 101: 399, 1929.
3. Parade: Herzstromkurven eineiiger Zwillingen, *Ztschr. f. klin. Med.* 128: 114, 1935.
4. Bakst, H. J., Wetherbee, W., and Foley, J. A.: Orthostatic Albuminuria in Homologous Twins, *New England J. Med.* 214: 832, 1936.
5. Comeau, W. J., and White, P. D.: Body Build and Heart Size, *AM. HEART J.* 17: 616, 1939.

THE PROBLEM OF ANGINA PECTORIS IN THE NEGRO*

MORRIS M. WEISS, M.D.

LOUISVILLE, KY.

THERE are numerous comments in the literature on the rarity of angina pectoris in the negro.^{1, 2, 3, 4, 5, 6} Most clinicians in the southern part of the United States are in accord that it is infrequently encountered in this race. Does the infrequency of angina pectoris in the negro indicate a white racial susceptibility to the disease? Roberts⁴ attributes the difference in incidence to the lack of mental stress and strain in the negro. Schwab and Schulze⁵ believe that it is due to an inherent difference in the sensitivity of the nervous systems in the two races. In a recent study, however, of the clinical manifestations of essential hypertension among negroes and whites admitted to the wards of the Louisville City Hospital,⁷ we found that angina pectoris was uncommon in both races. A history of angina pectoris was obtained in 0.5 per cent of the negro and only 1.5 per cent of the white patients.

Uncomplicated angina pectoris, of course, does not often require hospitalization. Moreover, the myocardial, cerebral, and renal failure symptoms of the hospitalized patient could obscure all history of cardiac pain. For these reasons it was decided to study the incidence of angina pectoris in negro patients with essential hypertension attending the outpatient department of the Louisville City Hospital, using, for comparison, a group of white patients with hypertension admitted to the clinic during the same period. This municipal clinic accepts only ambulatory and absolutely indigent individuals. Most of the clientele of the clinic are in the lowest intellectual and social scale of life. Patients with essential hypertension were selected for study because of the high incidence of angina pectoris in association with this disease.

The records of 324 negroes with essential hypertension, including only adults over 20 years of age, who were admitted consecutively to the outpatient department, were analyzed and compared with those of 246 white patients admitted to the clinic during the same period. Table I shows the age and sex distribution of the patients. There were 137 negro men, 187 negro women, 132 white men, and 114 white women. A history of angina pectoris was obtained in 9, or 2.8 per cent, of the negroes, and in 12, or 4.8 per cent, of the white patients. There were 3 negro males, 6 negro females, 8 white males, and 4

*From the Department of Medicine, School of Medicine, University of Louisville, Louisville, Ky.

Received for publication Nov. 12, 1938.

white females with the syndrome. Thus the incidence was low in both races. These figures are comparable to those reported by Flaxman,⁸ who found angina pectoris in 2.5 per cent of 430 white patients and 0.5 per cent of 193 negro patients with hypertensive heart disease in the various charity wards and clinics in Chicago. In contrast is the reported incidence in private patients. White⁹ obtained a history of angina pectoris in 26 per cent, and Nuzum, Elliot, and Evans¹⁰ in 12 per cent of persons with essential hypertension encountered in private practice.

TABLE I

AGE AND SEX DISTRIBUTION OF OUTPATIENTS WITH ESSENTIAL HYPERTENSION IN NEGRO AND WHITE RACES

AGE	NEGROES (324 CASES)			WHITES (246 CASES)		
	M	F	TOTAL	M	F	TOTAL
20-29	1	3	4			
30-39	9	30	39	3	8	11
40-49	27	54	81	11	16	27
50-59	50	65	115	41	47	88
60-69	30	29	59	53	32	85
70-79	18	6	24	22	10	32
80-89	2		2	2	1	3
	137	187	324	132	114	246

It is noteworthy that when the incidence of angina pectoris is low in the negro it is similarly low in the white patients from the same clinic. Stone and Vanzant,² who did not find a single instance of angina pectoris in negroes with heart disease, state that it is likewise not seen very frequently in the whites who attend the charity clinic, whereas among private patients it is fairly common. Gager,¹¹ in his private patients with heart disease, found that .10.9 per cent had angina, in contrast with 5.4 per cent in his charity practice. In the negro group of charity patients the incidence of angina was 4.5 per cent.

It is also noteworthy that in the literature on angina pectoris there are numerous comments on the comparative infrequency with which it is encountered in charity patients. Allbutt¹² states: "In my experience, its incidence among the laboring classes in Leeds was not remarkably high." Osler¹³ comments: "Though occurring among the poor, it is more frequently met with among the rich, or in persons of easy circumstances." Gallavardin¹⁴ claims that professional and well-to-do people are more frequently affected. Recent reports on relatively large numbers of cases, such as that of White and Bland,¹⁵ and Brooks,¹⁶ are based entirely on private patients. Czyhlarz¹⁷ feels that this social difference in the incidence of the disease can be explained on a difference in sensitivity of nervous systems. Hamman¹⁸ believes that angina pectoris will always be a disease of the refined, intellectual classes, since its effects are keenly appreciated and fluently

described by the intellectually alert, but not clearly perceived or described by the intellectually obtuse.

A disparity in the incidence of angina pectoris in the white and colored races might be explained on a difference in associated pathologic changes. Studies on the racial incidence of coronary artery disease would indicate that marked coronary sclerosis is not as common in the negro as in the white race. Thus, Bruenn, Turner, and Levy¹⁹ found that 133 of 137 cases of advanced coronary sclerosis occurred in white persons, and only 4 in negroes, although the ratio of white to negro patients studied was 12 to 1. A study by Johnson²⁰ of the autopsy records of 400 patients more than 39 years of age showed that the incidence of marked coronary sclerosis was 24 per cent for white males, 9 per cent of negro males, 10 per cent for white females, and 4 per cent for negro females. From this he concluded that members of the white race are much more susceptible to coronary sclerosis than negroes.

Neither of these reports considered the incidence of hypertension in the cases studied, a factor which would materially influence the relative severity of coronary disease. With this factor in mind, an analysis was made of the macroscopic descriptions of the coronary vessels in the protocols of 177 negro and 178 white patients with essential hypertension who were autopsied at the Louisville City Hospital from 1930 through 1936. Table II shows the distribution of the cases as to race, age, and sex. Males predominated in both races, probably because of the relative ease with which permission can be obtained for an autopsy on a man. No patient in either race was less than 30 years of age. There was a greater incidence in the younger age groups of the negroes than in the whites.

TABLE II

AGE AND SEX DISTRIBUTION OF AUTOPSY CASES OF ESSENTIAL HYPERTENSION IN NEGRO AND WHITE RACES

AGE	NEGRO (177 CASES)			WHITE (178 CASES)		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
30-39	11	10	21	3		3
40-49	22	13	35	12	8	20
50-59	30	27	57	17	19	36
60-69	24	10	34	48	14	62
70-79	10	11	21	29	15	44
80-89	6	3	9	11	2	13
	103	74	177	120	58	178

Table III shows the incidence of severe coronary sclerosis and myocardial infarction in each race. Marked coronary sclerosis was found in 20 per cent of the negro males, 21 per cent of the white males, 31 per cent of the negro females, and 24 per cent of the white females. Over 7 per cent of the negroes had myocardial infarction, in contrast to 10 per cent for the whites. This indicates that there is no racial

difference in the incidence of advanced degrees of coronary sclerosis or of myocardial infarction in individuals with essential hypertension. Hence differing degrees of coronary disease cannot explain the disparity in the incidence of angina in the negro as compared with the white race.

TABLE III

INCIDENCE OF MYOCARDIAL INFARCTION AND SEVERE CORONARY SCLEROSIS IN AUTOPSY CASES OF ESSENTIAL HYPERTENSION, COLORED CONTRASTED WITH WHITE RACE

AGE	NEGRO				WHITE			
	SEVERE CORONARY SCLEROSIS		MYOCARDIAL INFARCTION		SEVERE CORONARY SCLEROSIS		MYOCARDIAL INFARCTION	
	M	F	M	F	M	F	M	F
30-39		1			1			
40-49	6	4	2		2	1		
50-59	5	9	3	2	2	4	2	1
60-69	6	4	5		12	1	4	5
70-79	2	4	1		6	7	6	
80-89	2	1			3	1	1	
	21	23	11	2	26	14	13	6

DISCUSSION

Explanations of the rarity of angina pectoris in the negro are inadequate because they do not take into account the fact that there is a similar low incidence in white patients who are of the same intellectual level. A lack of ability to fully describe and interpret the sensation of cardiac pain can entirely explain the infrequency with which the syndrome is encountered in the negro. This is the same explanation offered by Hamman¹⁸ to account for the social differences in the incidence of angina pectoris. It is of interest that the most satisfactory histories of angina in this study were obtained from patients who were above the intellectual level of the average patient attending the outpatient department. The economic depression necessitated their admission to a free clinic. Differences from the white race in susceptibility to mental strain, nervous system sensitivity, or pathologic changes in the heart do not furnish an adequate explanation. Such factors explain the absence of the syndrome in certain individuals in a homogeneous group, but they cannot account for the large difference in the incidence in negro charity patients and white private patients. While a disturbed emotional state can precipitate an anginal attack, a more than moronic intelligence is required to describe that attack. We do not find angina pectoris in the negro because he is unable to give an adequate description of the sensations which the attack produces. Every clinician knows how difficult it is to obtain a good history from a southern negro. A difference in nervous system sensitivity seems a plausible explanation. However, the negro is very susceptible to pain. Moreover, both white and negro patients who attend the same clinic cannot have a low threshold for

those stimuli, such as effort, cold, mental strain, and excitement, which precipitate an anginal attack in an intelligent white person.

SUMMARY

1. A study is presented of the problem of the relative infrequency of angina pectoris in the ambulatory negro with essential hypertension.

2. The incidence of angina pectoris is low in both negro and white patients with hypertension who attend the same outpatient clinic. The syndrome occurred in 2.8 per cent of 314 negro patients and 4.8 per cent of 246 white patients with essential hypertension.

3. No racial difference in the incidence of advanced degrees of coronary sclerosis or myocardial infarction in individuals with essential hypertension was found at autopsy.

4. A lack of ability to fully describe and interpret the sensation of cardiac pain can entirely explain the relative infrequency with which angina pectoris is encountered in the negro charity patient as compared with the white private patient.

REFERENCES

1. Wood, J. E., Jr., Jones, T. D., and Kimbrough, R. D.: Etiology of Heart Disease, *Am. J. M. Sc.* 172: 185, 1926.
2. Stone, C. T., and Vanzant, F. R.: Heart Disease as Seen in a Southern Clinic, *J. A. M. A.* 89: 1473, 1927.
3. Davison, H. M., and Thoroughman, J. C.: Study of Heart Disease in the Negro Race, *Southern M. J.* 21: 464, 1928.
4. Roberts, S. R.: Nervous and Mental Influences in Angina Pectoris, *AM. HEART J.* 7: 21, 1931.
5. Schwab, E. H., and Schulze, V. E.: Heart Disease in the American Negro in the South, *AM. HEART J.* 7: 710, 1932.
6. Laws, C. L.: Etiology of Heart Disease in Whites and Negroes in Tennessee, *AM. HEART J.* 8: 608, 1932-33.
7. Weiss, M. M., and Prusmack, J. J.: Essential Hypertension in the Negro, *Am. J. M. Sc.* 510-516, 1938.
8. Flaxman, Nathan: Course of Hypertensive Heart Disease, *Ann. Int. Med.* 10: 748, 1936.
9. White, P. D.: A Note on the Common Occurrence of Serious Involvement of the Heart in Hyperpiesia, *New England J. Med.* 214: 719, 1936.
10. Nuzum, F. R., Elliot, A. H., and Evans, R. D.: Clinical and Pathological Study of Coronary Sclerosis: Its Incidence in Hypertension and Angina Pectoris, *AM. HEART J.* 10: 367, 1935.
11. Gager, L. T., and Dunn, W. L.: Heart Disease in Washington, D. C., *Med. Ann. District of Columbia* 2: 113, 1933.
12. Allbutt, Sir C.: Disease of the Arteries Including Angina Pectoris, Vol. 2, p. 253, London, 1915, The Macmillan Co.
13. Osler, W.: Lectures on Angina Pectoris and Allied States, New York, 1897, D. Appleton and Co.
14. Gallavardin, Louis: Les Angines de Poitrine, p. 40, Paris, 1925, Masson & Cie.
15. White, P. D., and Bland, E. F.: Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis, *AM. HEART J.* 7: 1, 1931.
16. Brooks, H.: Concerning Certain Phases of Angina Pectoris, Based on a Study of 350 Cases, *Am. J. M. Sc.* 182: 784, 1931.
17. Czyhlarz, E.: Zur Lehre der Angina Pectoris, *Wien. med. Wehnschr.* 74: 2541, 1924.
18. Hamman, L.: Symptoms of Coronary Occlusion, *Bull. Johns Hopkins Hosp.* 38: 273, 1926.
19. Bruenn, H. G., Turner, K. B., and Levy, R. L.: Notes on Cardiac Pain and Coronary Disease, *AM. HEART J.* 11: 34, 1936.
20. Johnson, C.: Racial Differences in the Incidence of Coronary Sclerosis, *AM. HEART J.* 12: 162, 1936.

ABSENCE OF PULSE IN THE VESSELS OF THE UPPER EXTREMITIES AND NECK IN ANEURYSM OF THE AORTIC ARCH

ELMER MAURER, M.D.

CINCINNATI, OHIO

THE complete absence of pulsation in the radial, brachial, and carotid arteries bilaterally is a rare condition. Two patients presenting such abnormalities have been under observation and subsequently have come to autopsy in the Cincinnati General Hospital. A study of the literature reveals that just five similar cases of pulse absence in aortic aneurysm have been reported previously and that in only three of these was there a post-mortem examination.

Hare and Holder,¹ in 1899, analyzing 953 cases of aortic aneurysm with special reference to pulse abnormalities, found that in only thirty-two out of 784 cases of aneurysm of the aortic arch was there any pulse abnormality at all, and in only five of these was there complete absence of the radial pulse on one side. In the large series of 4,000 cases collected and reviewed by Boyd,² in 1924, no case of complete absence of carotid or radial pulse was recorded. In the literature of the past twenty years, including the articles by Findlay,³ Arnold,⁴ and Kahn,⁵ much space has been given to the consideration of pulse inequalities, but little mention has been made of such observations as are under discussion here. The only exception to the general lack of discussion of absence of arterial pulsation is Osler's⁶ mention of a reported case of complete obliteration of the pulse in the arteries of the head and upper extremities in a patient with a large aneurysm of the arch of the aorta. Furthermore, it should not go unnoticed that Osler⁷ mentions an instance of obliteration of the pulse in the abdominal aorta and in both lower extremities in the presence of aneurysm of the abdominal aorta.

According to Hirschfelder, Harvey was the first to report obliteration of the pulse in aneurysm of the thoracic aorta. Subsequently, throughout the literature inequality and retardation of the pulses were frequently referred to, while complete obliteration was seldom described. Lamb,⁸ in 1920, for instance, in an analysis of ninety-two history records, reported thirteen cases in which there was inequality of pulses, and later, in 1924, Dr. Morris H. Kahn⁵ published a treatise and case report dealing with delayed radial pulses in aortic aneurysm.

Cohen and Danie,⁹ in 1933, when reporting their own case of bilateral pulse absence in aortic aneurysm, made mention of only four similar re-

From the Department of Pathology, University of Cincinnati and the Cincinnati General Hospital.

Acknowledgment is made to the Department of Medicine, Cincinnati General Hospital, for the use of clinical records.

Received for publication Nov. 16, 1938.

ports in the literature. In but two of these cases were post-mortem examinations performed. The first report, that of Broadbent¹⁰ (1875), described the absence of both radial pulses and of the right carotid pulse, all of which was accounted for by a plaque of atheroma almost completely obliterating the orifice of the innominate artery, which was unusually close to the left common carotid artery. An anomalous vertebral artery, arising directly from the aortic arch, encroached upon the orifice of the left subclavian artery, which likewise was further narrowed by an atheromatous plaque. The lesions therefore were multiple.

In the second case, reported by Shikhare,¹¹ in 1921, there was absence of the pulses as a result of almost complete obliteration of the lumina of the large vessels arising from the aortic arch by ante-mortem thrombi, which arose as fingerlike projections from a "mother" clot filling the greater portion of the dilated aortic arch.

In the two remaining cases, those of Crawford¹² and Kampmeier and Neumann,¹³ there was no post-mortem examination, so that the pathologic basis for the obliteration of the pulses necessarily remained a matter of conjecture. It was suggested, however, by Kampmeier and Neumann that in Crawford's case, as well as in their own, the obliteration of the arterial pulses was probably produced by pressure of an enlarging aneurysmal sac on the arterial trunks.

In Cohen and Danie's⁹ own case of bilaterally absent carotid and radial pulses, post-mortem examination disclosed a fusiform aneurysm of the ascending and transverse "arms" of the thoracic aorta, with complete obliteration of the three main arteries arising from the aortic arch, their sites being represented merely by two shallow depressions. Microscopic examination of sections taken through the sites of occlusion showed extensive subintimal proliferation in the innominate, left subclavian, and left carotid arteries. Although syphilitic endarteritis is admittedly rare in large arteries, these investigators ventured the opinion that occlusion of the large vessels came about through narrowing of their orifices by plaques associated with syphilitic subintimal proliferation.

The first case here reported was recently observed in the Cincinnati General Hospital. It was of unusual interest because of the absence of pulsations in the superficial arteries of the right arm and both carotids, and of importance in that the pathologic findings were different from any so far recorded. Interest being aroused as to the incidence of this unusual condition, the clinical and necropsy records of all patients coming to post mortem in the Cincinnati General Hospital during the past eleven years, 1927 to 1937, inclusive, were reviewed. In a total of 7,455 autopsies performed during this period, 113 cases of aneurysm of the aortic arch were encountered, in five of which there was complete absence of pulse in one or more of the superficial vessels of

the upper extremity and neck. In two there were pulse differences only in the upper extremities, and in the entire series only one case was discovered in which there were no recognizable pulsations in the radial and carotid vessels bilaterally. This is included as Case 2 of the present report.

REPORT OF CASES

CASE 1.—History: M. J., 65 years of age, a colored woman, was brought to the Cincinnati General Hospital, Feb. 3, 1938, unaccompanied by either relatives or friends. On admission to the receiving ward the patient could give no history, for she was unable to talk; her entire right side was paralyzed. The history, therefore, necessarily was obtained subsequently from a woman with whom the patient had been residing during the past year. According to this informant, the patient had always enjoyed fair health until Jan. 24, 1937, when, while sitting in a chair, she suddenly slumped forward, and on being examined immediately thereafter was found to be without the power of speech and paralyzed over her entire right side. The patient was placed in bed, and the following morning could respond to questions and make active movements with her right arm and leg. Following this episode she was again up and about until Feb. 2, 1938, the day before admission, when again, while sitting in a chair, she suddenly fell to the floor unconscious, was again put to bed; the following day, on advice of a local physician, she was brought to the hospital. No further history was obtainable.

Examination.—Physical examination, a short time after admission on the neurologic ward, revealed an aged, semiconscious, thin, little colored woman who was unable to talk or to move her right arm and leg. Her head was retracted laterally to the left and the neck became rigid when forceful flexion to the right was attempted. The right margin of the mouth drooped downward, the right side of the body was flaccid, the left arm and hand moved spasmodically, and the left leg was flexed on the thigh. The only obtainable response to external stimuli was a withdrawal movement of the left upper and lower extremities following pinprick. Respirations were Cheyne-Stokes in character, labored and noisy. The skin generally was dry, scaly, and much warmer over the left side of the body.

Cursory examination of the head revealed no evidences of recent or past trauma. The pupils were equal, regular, moderately dilated, and reacted well to light and in accommodation. No nystagmus or strabismus was noted. Ophthalmoscopic examination showed the disks to be clearly outlined and without papilledema. There were well-marked, bilateral, retinal arteriosclerosis and notching of veins by arteries which crossed them.

The right margin of the mouth dropped and the left lip was full and relaxed. The lower jaw was edentulous, the pharynx was clear, and the tongue deviated to the left of the midline.

There was a torticollis deformity on the left, with prominence of the right sternocleidomastoid muscle and complete absence of pulsations in both carotid vessels.

The chest was symmetrical and the respiratory excursions equal, jerky, and variable. A few dilated veins were easily visible over the anterior surface of the upper third of the left chest. The lungs were normal to percussion and auscultation.

The cardiac apex impulse, which was forceful, heaving, and diffuse, was easily visible in the sixth intercostal space in the midaxillary line, 15 cm. from the mid-sternal line. There was a palpable pulsation in the third right intercostal space, approximately 6 cm. from the midline. On percussion, the heart was thought to be greatly enlarged to the left, and an area of parasternal dullness 9 cm. wide was found at the level of the first interspace. The arch of the aorta was slightly above the suprasternal notch and presented itself as a firm, pulsating, globular mass. A soft systolic thrill was felt over the cardiac apex, and a loud, harsh, rasping systolic murmur

was audible over the same area. An inconstant soft, blowing, systolic murmur could be heard over the base of the heart. No diastolic murmurs were present. The cardiac mechanism was normal except for numerous extrasystoles. The pulse at the right wrist was barely perceptible and so weak that estimation of its rate was impossible. The left radial pulse was 94 per minute, strong, and of good volume. The blood pressure in the right arm was 100/90 and in the left arm 190/100, both readings being obtained with the patient lying supine in bed. The vessels in all four extremities presented a diffuse sclerosis of the Mönckeberg variety.

Abdominal, pelvic, and rectal examinations were essentially negative.

The cranial nerves were intact except for right-sided facial hemiparesis and lingual deviation to the left. The deep reflexes were slightly hyperactive on the left, the abdominal reflexes depressed on the right, and plantar reversal signs were not obtained. Motor power was completely gone in the right upper and lower extremities and the right side of the face.

The clinical impression at this time was that the patient had suffered a cerebrovascular accident on the left side, due to thrombosis, with resultant right-sided hemiplegia and facial weakness. To this were added the diagnoses of aortic dilatation with aneurysm of the arch and compression of the innominate and left common carotid arteries, and left-sided torticollis.

A note made in the clinical record on February 4 described the patient as able to respond at times and as having persistent right-sided flaccid hemiplegia and facial paralysis. Positive Oppenheim and Chaddock signs were obtained for the first time, but the Babinski response remained flexor in type bilaterally. The left radial pulse was full and the blood pressure in the left arm was recorded as 200/100. The right radial pulse was still imperceptible and the blood pressure reading in this arm was noted as 90/85. The other signs remained unchanged.

Laboratory Reports.—Urine and stool examinations were negative on several occasions. Blood studies on admission showed that the hemoglobin was 15.6 grams, the erythrocyte count 5,700,000, and the leucocyte count 15,650, with 80 per cent neutrophils, 11 per cent lymphocytes, and 9 per cent monocytes. Blood chemical analyses two days after admission showed a urea of 42 mg. per cent and carbon dioxide combining power of 32 volumes per cent. The blood Kahn reaction was one plus. Clear spinal fluid released under an initial pressure of 15 cm. of water contained three cells, all lymphocytes, per c.mm. and gave a negative Pandy test. The spinal fluid Wassermann and Meinicke reactions and gold curve were all negative. Electrocardiographic tracings made on the patient's second hospital day indicated mild myocardial damage. Fluoroscopic and radiographic examination on the same day showed moderate enlargement of the heart to the left and a fusiform widening of the superior mediastinum, with displacement of the trachea to the left. This superior mediastinal mass was seen to pulsate under the fluoroscope and was thought to be a large aneurysm of the ascending aorta, with some involvement of the innominate artery. The lung fields were clear.

During her short stay in the hospital the patient was treated with supportive measures, but gradually became unresponsive, sank into a deep stupor, and died on Feb. 6, 1938, three days after admission and five days after the onset of her illness.

Necropsy.—Superficial examination of the body was essentially negative except for the left-sided torticollis deformity. On removing the breast plate there was encountered a globular mass, approximately 7.5 by 8 by 8 cm. in diameter, projecting anteriorly and upward from the superior portion of the anterior mediastinum. This mass was of unusual firmness, saccular in shape, and occupied all available space between the origin of the left common carotid artery and the first portion of the transverse aortic arch. Examination of the aneurysmal sac through a small window made in its anterior surface showed the lumen to be completely filled with an organized, laminated, ante-mortem thrombus. The left common carotid artery

at its origin was completely occluded by what appeared to be a cicatricial mass centering about the carotid ostium, and sealing together the intimal coverings in the first centimeter of its course. Immediately above its origin the left common carotid artery presented its usual size and possessed normal elasticity. It was impossible to determine definitely in the gross whether the occlusion was due to cicatricial stenosis caused by inflammation, compression by the aneurysmal mass, or both. Furthermore, it was impossible to identify the origin of the innominate artery; the only remnant of it was a small obliterated tubular structure coursing along the upper right side of the posterior surface of the aneurysm. The bifurcation of the innominate artery into the right common carotid and subclavian arteries, however, could be identified near this area, and the course of the innominate vessel traced toward the heart over the posterior surface of the aneurysm for a distance of 3.5 cm. Beyond this point the innominate artery, after coursing a distance of 0.5 cm. as an



Fig. 1.—Aneurysm of the arch of the aorta, showing occlusion of the ostium of the left common carotid artery (Case 1).

obliterated tubule, was lost in the posterior wall of the aneurysmal mass. Arising from the anterior inferior wall of the terminal portion of the transverse aortic arch was another smaller, shallow, saucer-shaped aneurysm, 3 cm. in diameter and 1 cm. deep. Within the ascending and transverse segments of the arch of the aorta the intimal surface was almost entirely occupied by puckered, pearly-white scars and atheromatous plaques.

The heart was moderately enlarged, flabby, weighed 500 gm., and was pushed to the left and backward by the aneurysm. The valve leaflets were all competent, and the mural endocardium was smooth and glistening.

The trachea and esophagus were patent and showed no evidences of compression or erosion.

The kidneys were remarkable only for moderate arterial and arteriolar nephrosclerosis.

The pia-arachnoid over the convexity of the cerebral hemispheres of the brain, which weighed 1075 gm., showed patchy areas of milky opacity which were interpreted as the result of chronic leptomeningitis. The cerebral veins were congested and numerous atherosclerotic rings were seen in the vessels of the arterial circle of Willis. The left internal carotid and left middle cerebral arteries at their point of juncture with the arterial circle were completely occluded by an ante-mortem thrombus which extended for a distance of 3 cm. into the latter vessel. Microscopic examination of numerous sections of both vessels at their point of anastomosis with the arterial ring and at regular intervals along the first 2 cm. of their courses disclosed that their lumina were completely filled with a recent thrombus composed of corallike laminae of platelets with marginal leucocytes and intervening red corpuscles and fibrin. The intimal layers in all sections



Fig. 2.—Posterior view of the same specimen as in Fig. 1, showing occlusion of the innominate artery.

were markedly thickened and showed extensive atheroma, and also military erosions of the endothelial lining, covered by thrombi, and hyalinization of the new connective tissue which bulged from the arterial walls for some distance into their occluded lumina. Horizontal section through the brain at the level of the basal nuclei revealed a recent, massive, wedge-shaped area of infarction replacing the greater portion of the left temporal lobe, involving the anterior left caudate nucleus, the internal capsule in its entirety, the lenticular nucleus, thalamus, and island of Reil, extending posteriorly to involve the anterior extremities of the optic tract. Even with definite microscopic proof of the existence of an ante-

mortem thrombus in the internal carotid and middle cerebral arteries it is difficult, if not impossible, to explain with certainty the origin of the occluding clot. From the data at hand, however, two feasible explanations can be offered. The occlusion could have occurred because of: (1) embolus originating in the aneurysmal thrombus and passing by way of the left subclavian and vertebral arteries to the point of occlusion; or (2) thrombosis of the middle cerebral artery resulting from intimal damage due to arteriosclerosis. However, it would seem very unlikely that an embolus would seek out such a circuitous pathway as is described by the right-angled origin and spiral course of the left vertebral artery. This improbability and the lack of embolic phenomena in the remaining viscera would tend to support the second possibility.

Histopathology.—The histologic examination of the aortic arch and its major vessels was carried out on sections stained by (a) hematoxylin and eosin, (b) hematoxylin and Van Gieson, and (c) Levaditi's stain. Transverse sections through the arch of the aorta and the innominate and left common carotid arteries at their points of occlusion showed marked intimal proliferation, hyalinization, ulceration, and necrosis, overlying a distorted, scarred media dotted with localized areas of necrosis and cellular infiltrate composed for the most part of numerous lymphocytes, plasma cells, and foreign-body giant cells. In several places these cellular accumulations assumed the form of miliary gummas. Similar, smaller, but well-defined, areas of necrosis and lymphocytic infiltration were seen in the adventitial coats of all the occluded vessels, the cellular elements being arranged in the form of perivascular lymphocytic "collars" about the vasa vasorum. The whole of the intimal bundle in all sections stained a definite pink with Van Gieson's stain. Levaditi preparations failed to reveal any spirochetes.

CASE 2.—History: M. M., 33 years of age, a colored woman, was brought to the receiving ward of the Cincinnati General Hospital, Sept. 30, 1933, shortly after being discovered unconscious on the street. According to the history obtained from a daughter, the patient had suffered a "stroke" with resultant right-sided hemiplegia and complete aphasia three and one-half years prior to her present accident. In the interim she had regained some use of her right arm and leg, could say a few words, and apparently was enjoying fair health except for numerous fainting spells. These latter seizures were described as periods of complete unconsciousness during which the patient appeared to be lifeless except for respirations. She had received a small amount of antisyphilitic treatment before admission. The patient had lost 40 pounds during the preceding two years. The hospital course was uneventful except for three or four attacks of syncope and weakness brought on by sitting upright and relieved by lying down. Approximately two months after admission the patient suddenly sat up in bed, expectorated three ounces of blood, and twenty minutes later died.

Examination.—The patient was a well-developed colored woman apparently comfortable in bed while lying down. The skin over the shoulder girdle, upper extremities, head, and neck was less warm than over the rest of the body. The lips and nail beds were cyanotic. The right pupil was slightly larger than the left, but both reacted well to light and in accommodation. Examination of the neck showed diffuse enlargement of the thyroid gland, deviation of the trachea to the right, no tracheal tug, and absent pulsations in both carotid arteries. Except for slight lifting of the upper sternum with each heart beat the chest was essentially negative. Parasternal dullness was present on both sides in the first and second intercostal spaces. The cardiac apex was visible in the fifth left intercostal space 11 cm. from the midsternal line. No murmurs could be heard, the aortic second sound was louder than the pulmonic second, and the heart sounds were of "tic-tac" quality. No pulse could be felt in either upper extremity and the blood pressure could not be measured in the arms. In the lower extremities a systolic pressure of 120 was noted on several

occasions. Dorsalis pedis pulsations were present bilaterally. Pelvic examination revealed a large fibroma of the uterus. The arms and hands on both sides were definitely atrophic.

Laboratory Reports.—Examination of the urine and stools yielded negative results on all occasions. The blood showed a hemoglobin content of 80 per cent, an erythrocyte count of 5,400,000, and a leucocyte count of 7,500, with a normal blood smear. The blood Wassermann reaction was strongly positive. The spinal fluid showed a trace of globulin and three cells per c.mm. The spinal fluid Wassermann reaction was positive and the gold curve was reported as 0013443211. The basal metabolic rate was minus 6 per cent. The roentgenologist reported marked prominence of the aortic knob and thickened pleura over the right apex.

Necropsy.—The body was that of a well-developed, moderately obese colored woman of middle age. On removing the heart a firm mass, 5 by 5 cm. in diameter, was encountered in the upper mediastinum, which was identified as a saccular outpouching of the transverse arch of the aorta, filled with a laminated blood clot. The aortic intima in this region showed scattered, elevated, tough, pearly-white plaques edged with a thin rim of scar tissue.

Glove-finger projections of the ante-mortem thrombus situated in the aneurysm extended into and completely occluded the innominate, left common carotid, and left subclavian arteries. The vessels distal to the aneurysm showed no noteworthy change. There was no ulceration by the aneurysm into the esophagus or trachea. The remaining macroscopic findings were not significant except for caseous pneumonia, purulent bronchitis, and focal areas of cerebral encephalomalacia.

Histopathology.—Microscopic examination of representative sections of the aorta showed fibrous thickening of the intimal lining, with fragmentation and lymphocytic infiltration of the media. The vasa vasorum of the adventitia presented the usual perivascular lymphocytic "collars" seen in syphilitic aortitis.

DISCUSSION

In view of the complete occlusion of the large arterial trunks which carry blood to the head, neck, and arms, it would have been interesting to have traced out the possible channels of collateral circulation. However, such detailed dissection of the anastomoses in the neck and arms would have necessitated special autopsy permission which unfortunately was not obtained in the two cases here reported.

It is interesting to note that in all of the five previously reported cases the diagnosis of syphilis could be made either on the basis of post-mortem findings or serologic tests. In Broadbent's case there was a positive history of syphilis and characteristic lesions were demonstrated in the aorta. In Crawford's and in Kampmeier and Neumann's cases the serologic tests were positive for syphilis and the diagnosis was said to have been verified roentgenologically. No serologic data were available in Shikhare's report, but a definite aneurysm was demonstrated post mortem. Both gross and microscopic evidences of syphilis were presented in the case reported by Cohen and Danie. Positive serologic tests and gross and microscopic lesions of syphilis occurred in both cases here reported.

Of further interest is the fact that the presenting complaint in all cases, both those reviewed and those here reported, was referable to the cerebrum, evidently caused by cerebral anoxemia.

In all cases presented there was complete absence of pulsations in the carotid and radial vessels, with the exception that a weak carotid pulse was present on one side in Broadbent's patient and a radial pulse in the left arm in the first case reported here. Incidentally, it should be noted how, in this same patient, the collateral circulation reached such a degree of perfection that a blood pressure of 100/90 could be measured in the right arm; which was later shown, anatomically, to be completely without any main arterial supply.

SUMMARY

Two cases of aneurysm of the aortic arch with absent carotid and radial pulses are reported. In a review of the literature but five similar cases were found, in only three of which was there a post-mortem examination. Syphilis was undoubtedly present in all of these cases. The clinical picture in all of the cases was that of cerebral disease, with attacks of dizziness and syncope, together with absent pulsations in the superficial vessels of the neck and upper extremities.

REFERENCES

1. Hare, H. A., and Holder, C. H.: Some Facts in Regard to Aneurysm of the Aorta, *Am. J. M. Sc.* 118: 399, 1899.
2. Boyd, L. J.: A Study of Four Thousand Reported Cases of Aneurysm of the Thoracic Aorta, *Am. J. M. Sc.* 168: 654, 1924.
3. Findlay, L.: On Delay or Retardation of the Pulse as a Sign of Aneurysm, *Practitioner* 83: 803, 1909.
4. Arnold, H. D.: Importance of the Early Detection of Aneurysm of the Aorta, *Am. J. M. Sc.* 135: 515, 1908.
5. Kahn, M. H.: Pulse Difference in Aneurysm of the Arch of the Aorta, *M. Clin. North America* 8: 347, 1924.
6. Osler, Wm.: *Modern Medicine*, Vol. 4, p. 864, Philadelphia, 1927, Lea and Febiger.
7. Osler, Wm.: *Principles and Practice of Medicine*, Ed. 8, p. 853, 1912, New York, Appleton and Co.
8. Lamb, A. R.: *Nelson's Loose Leaf Living Med.* 4: 552, 1920.
9. Cohen, H., and Danie, T. V.: Bilateral Obliteration of Radial and Carotid Pulses in Aortic Aneurysm, *Lancet* 1: 852, 1933.
10. Broadbent, W. H.: Absence of Pulsations in Both Radial Arteries the Vessels Being Full of Blood, *Tr. Clin. Soc. London* 8: 165, 1875.
11. Shikhare, P. V.: Notes on a Remarkable Case of Absence of Pulsation in the Arteries of the Upper Parts of the Body, *Indian. J. Med.* 2: 526, 1921.
12. Crawford, J. R.: Bilateral Pulse Obliteration in Thoracic Aneurysm, *J. A. M. A.* 76: 1395, 1921.
13. Kampmeier, R. H., and Neumann, V. F.: Bilateral Absence of Pulse in the Arms and Neck in Aortic Aneurysm, *Arch. Int. Med.* 45: 513, 1930.

ELECTROCARDIOGRAPHIC CHANGES INDUCED BY THE TAKING OF FOOD

A PRELIMINARY REPORT

MANUEL GARDBERG, M.D., AND JENNY OLSEN, B.A.
NEW ORLEANS, LA.

ALTHOUGH Wilson and Finch¹ reported certain transient changes following the ingestion of ice water, there are, as far as we have been able to ascertain, no reports in the literature concerning the effect on the electrocardiogram of taking food. An investigation of this matter was undertaken by us, early in 1938, with the object of determining whether or not ordinary meals induce changes of sufficient magnitude to be taken into consideration in the clinical interpretation of electrocardiograms.

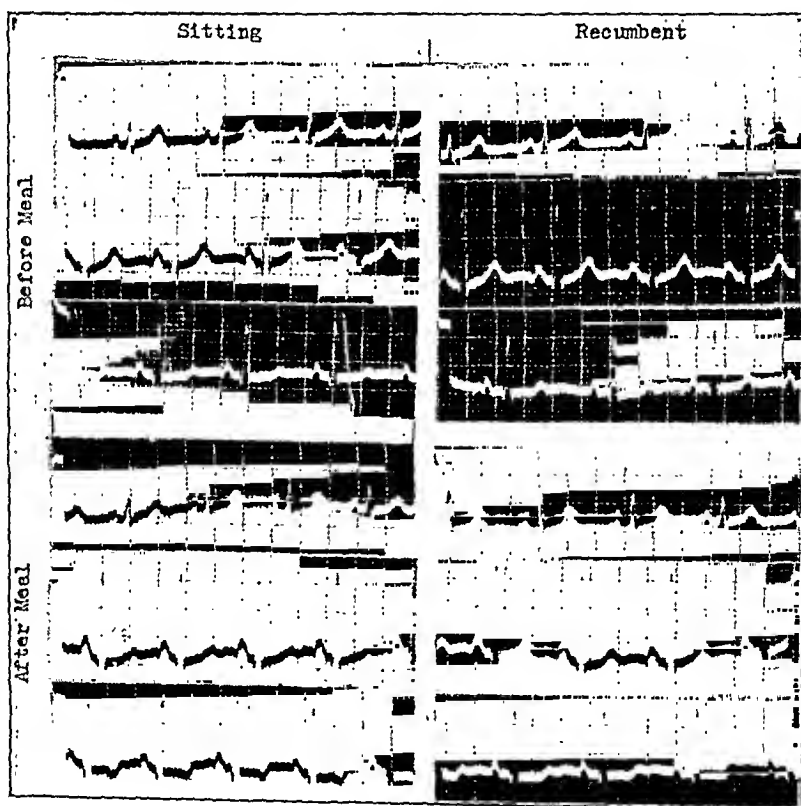


Fig. 1.

Electrocardiograms were made on nine normal, healthy, young adults before, and again within thirty minutes following, an ordinary mixed meal. Of these, seven showed changes which are of some in-

From the Department of Medicine, School of Medicine, Tulane University, New Orleans.
Received for publication Dec. 10, 1938.

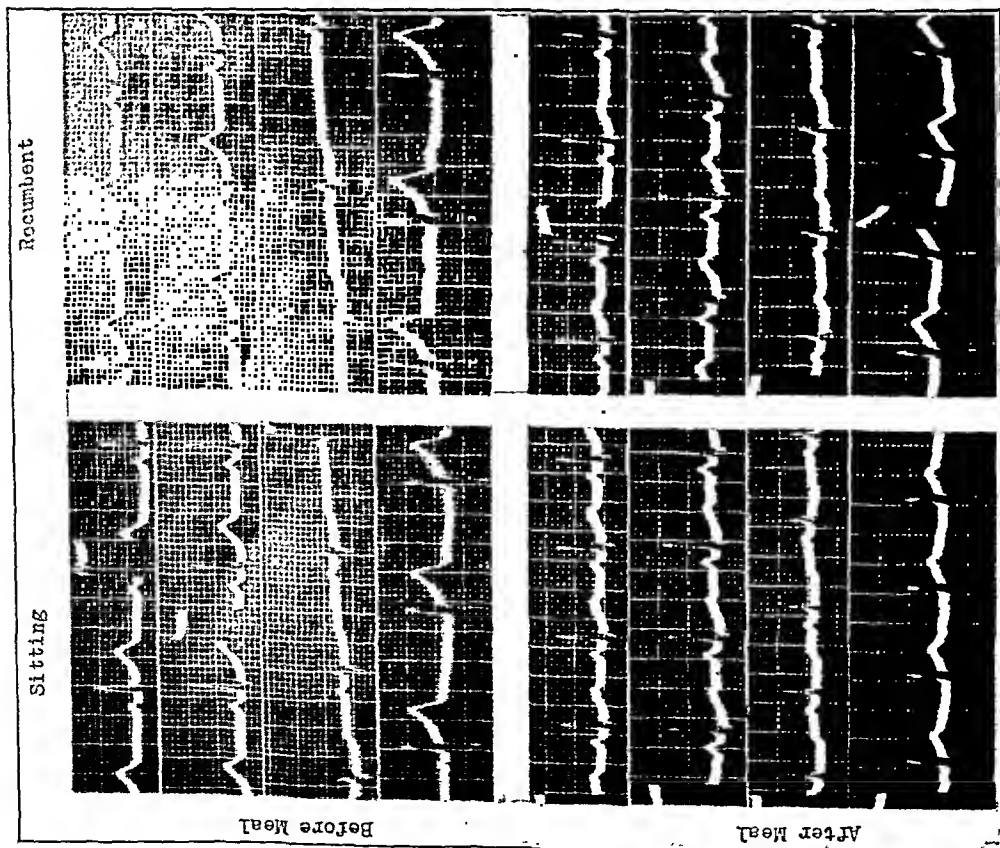
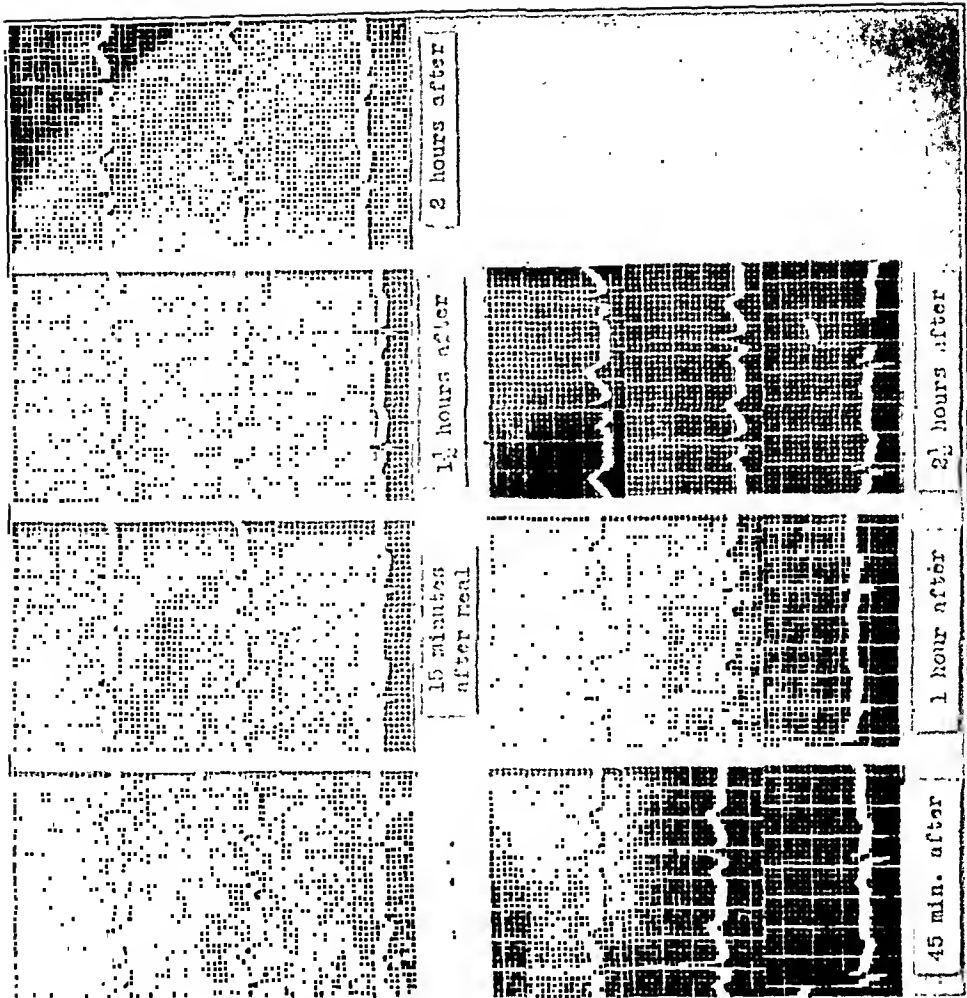


Fig. 2.



terest. These changes consist of a 30 to 50 per cent decrease in the height of the T-waves in Lead I or III, or in all three leads. In one case (Fig. 1), T_3 , which was previously upright, became inverted. In another (Fig. 2), T_1 not only was markedly lowered, but became notched also.

Thus far the cause of these changes has not been determined. They cannot be correlated with change in heart rate, for in one case the rate remained the same. Again, the change in the T-wave is not proportionate to the degree of rate change in any case. In no case did sufficient change in the electrical axis occur to explain the alterations in the height of the T-waves.

Several subjects have been studied in an attempt to discover the time of onset, and duration, of these changes. It has been found that the change does not reach its maximum until about one hour after the food is taken. It persists at this level for one and one-half to two hours, and then begins to disappear (Fig. 3).

CONCLUSION

Though no final conclusion is possible at the present time, it seemed justifiable to render a preliminary report of the finding of certain changes in the electrocardiogram, following the taking of food, in seven of nine normal individuals, together with the behavior of these changes with respect to onset and duration in several other (also normal) individuals.

REFERENCE

1. Wilson, F. N., and Finch, R.: The Effect of Drinking Iced-Water Upon the Form of the T Deflection of the Electrocardiogram, *Heart* 10: 275, 1923.

Department of Clinical Reports

PRIMARY TUMOR OF THE HEART (ENTRANCE OF THE PULMONARY ARTERY)*

CASE REPORT

W. C. MARTIN, M.D., E. L. TUOHY, M.D., AND CHARLES WILL, M.D.
DULUTH, MINN.

PRIMARY tumors of the heart are of sufficient rarity to merit report. The present instance concerns a woman, 46 years of age, who entered St. Mary's Hospital in obvious, severe, congestive heart failure, and died within thirty hours. Fortunately, there was time to observe her and to record some important data. There was a negative history of anything betokening rheumatic fever or its equivalent. There was no hypertension. While somewhat frail, she had never been conspicuously ill. She had had three children, with normal deliveries, the youngest of whom was 17 years old.

She had consulted her doctor about an upper respiratory infection early in October, 1937. During the succeeding winter she had lost six pounds, which reduced her weight to 102 pounds. She had noted increasing fatigue and dyspnea on slight exertion, but she had had no orthopnea. In March, 1938, her physician diagnosed hypochromic, microcytic anemia, and gave her extra vitamins and iron. A month later her hemoglobin was recorded as 43 per cent, and she felt no better. In keeping with this type of anemia, she had decidedly brittle and scaphoid finger nails, a smooth tongue, and a very indifferent appetite. A systolic murmur was heard at the base of the heart. Edema noticeable to the patient first appeared in the third week of May, 1938, and thereafter her discomfort and incapacity increased rapidly. There was conspicuous absence of precordial pain, and nothing comparable to angina of effort. A few days before entering the hospital there had been some sense of oppression and fullness in the abdomen. The dark color of the stools was thought to be a result of the iron medication, and this proved to be correct.

On the day of admission to the hospital her breathing was hurried, even, and non-stertorous, at a rate of about 36 per minute. There was a dusky pallor, lending a suggestion of the "café au lait" appearance. This, coupled with a very loud systolic murmur heard over the precordium and a history of severe anemia, led to a careful search for petechiae. None could be found, nor could the spleen be palpated. It was noted that she had extreme changes in the nails (koilonychia, brittleness), and that the tongue was smooth and showed some atrophy of the papillae, without actual glossitis. The liver was very easily palpable, and was down well below the costal margin. The neck veins were greatly distended, so much so that pressure upon the liver did not distend them any more. Unfortunately, we did not have the opportunity to measure the venous pressure; and in her semiconscious state we could not estimate the arm-to-tongue circulation time. The abdomen had a somewhat doughy feel, indicating some ascites. Over the base of the right lung the percussion note was dull to flat, and bronchial breathing and whispered pectoriloquy were present in this area. The apex thrust of the heart was out somewhat to the left. The blood pressure at that time was somewhat low (about 100/70). The eye grounds were entirely negative.

*From the Clinic and Pathological Laboratories of St. Mary's Hospital, Duluth, Minn.

Received for publication Nov. 4, 1938.

Differential Diagnosis.—The patient was suffering from congestive heart failure of high degree, from which she died very shortly, while an attempt was being made, by means of slow intravenous injection, to combat the acidosis which the carbon-dioxide combining power of 30 volumes per cent indicated.

With edema, some ascites, hepatic enlargement, evidence of fluid in the right pleural cavity, and low voltage in all leads of the electrocardiogram (she did have considerable fluid in the pericardial sac), was she in the *terminal stage* of congestive heart failure, with subacute bacterial endocarditis superimposed upon either an old rheumatic or congenital defect? With the type of anemia present, and the characteristic changes in the nails and tongue, one could be quite sure that this anemia was not secondary to subacute endocarditis. Examination of the blood just before death showed that the hemoglobin was 75 per cent, the erythrocyte count 4,900,000, the leucocyte count 13,800, and the differential count normal. These high counts imply hemoconcentration through dehydration and acidosis.

The loud basal systolic murmur raised the question of mitral valve involvement and indicated caution about attaching too much importance to anemia as a possible factor. The definite liver enlargement and the great engorgement of the veins of the neck indicated tricuspid regurgitation with right ventricular decompensation. The bedside roentgenogram gave confirmation of cardiac enlargement both to the left and right. The absence of any thrill, clubbing of the fingers, and history of cyanosis spoke against pulmonary stenosis of long duration. Further comment will be made later upon some of these items.

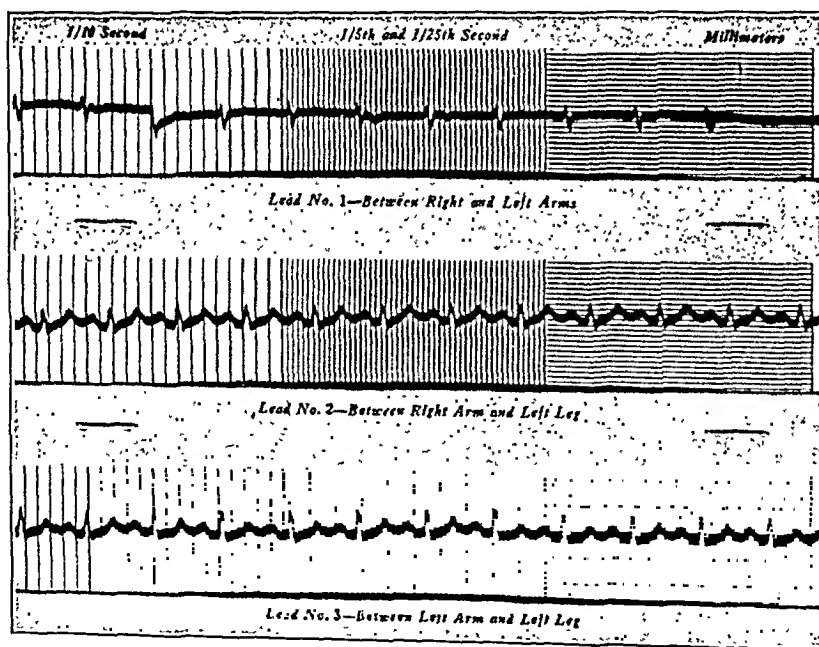


Fig. 1.—Electrocardiogram taken a few hours before the patient died. Low voltage and right axis deviation are noted. Isoelectric T in Lead I.

Dr. George L. Berdez, pathologist at St. Mary's Hospital, reported that on removing the sternum it was obvious that a very unusual condition obtained. The following is excerpted from Dr. Berdez' extensive and detailed protocol:

"Cardiac dilatation more to the right than to the left, with resultant extreme dilatation of the right ventricle. The aorta and the aortic valves were normal. On opening the right ventricle a polypoid tumor projected through the pulmonary orifice, producing at once high grade stenosis and moderate insufficiency. The growth was about $2\frac{1}{2}$ cm. in diameter. It had a grayish-white color, and varied from a

compact structure in some areas, to a softer and edematous consistency. Upon opening the pulmonary artery itself this whitish tumor was seen to actually involve the pulmonary valve, and to spread to the adjacent endocardium for a distance of about $2\frac{1}{2}$ cm. Sectioning the wall of the pulmonary artery, the tumor tissue was seen to invade its whole thickness, without, however, perforating it. The pulmonary valve invasion had rendered the cusps somewhat softened, thickened, to a thickness of 0.3 cm., or more. The tumor spread along the course of the pulmonary artery, to the right and to the left pulmonary arteries, and to the beginning of their main branches. The lumen of the right pulmonary artery was somewhat narrowed; those of the main branches of the left pulmonary artery were slightly dilated; the wall of these latter branches appeared somewhat thin, and the surface demonstrated faint longitudinal striae. No emboli were found. There was moderate emphysema of the left lung, but little else was demonstrated.



Fig. 2.—The heart is shown with the right ventricle opened. The diffuse tumor rises from the background of the opened pulmonary artery.

“Microscopically, the tumor cells were decisively polymorphous (irregular in size and shape); in places the cells were spindled, at others rounded. The cell nuclei were also irregular in shape and size (elongated, rounded, irregular), and were moderately rich in chromatin. Some of the nuclei were hypochromatic. Only a few showed mitoses. The development of a relatively few fibrillar cellular elements in some places accounted for the edematous areas; areas of connective tissue and fibrosis accounted for the firmer zones. The tumor cells invaded deeply into the wall of the artery, as was intimated in the growth. There was shown an occasional area of necrosis, with numerous Pmn's (polymorphonuclear leucocytes) associated. The adventitia of the pulmonary artery was edematous, and showed areas of lymphatic infiltration. Sections of the right pulmonary artery showed the tumor invading the intima, and the resultant thickening accounted for the tendency to stenosis. It was likely that the thinning out of the left pulmonary artery followed the insufficiency of the pulmonary valve. No metastases were found.”

The final diagnosis was neoplastic stenosis, grade III, of the pulmonary valve, with grade I insufficiency of the pulmonary valve; and marked hypertrophy and dilatation of the heart. The tumor proved to be a polymorphous cell sarcoma, with a very limited amount of fibrosis.

Fig. 3.

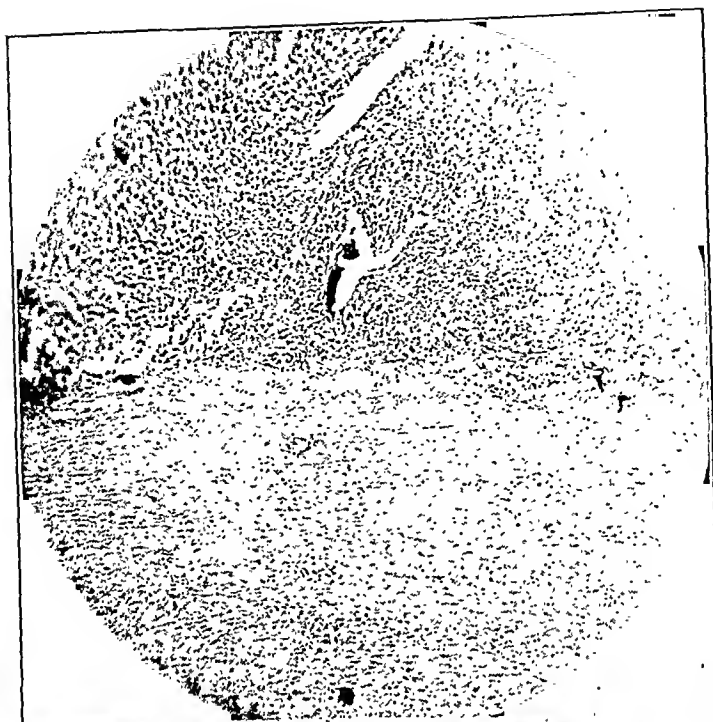


Fig. 4.

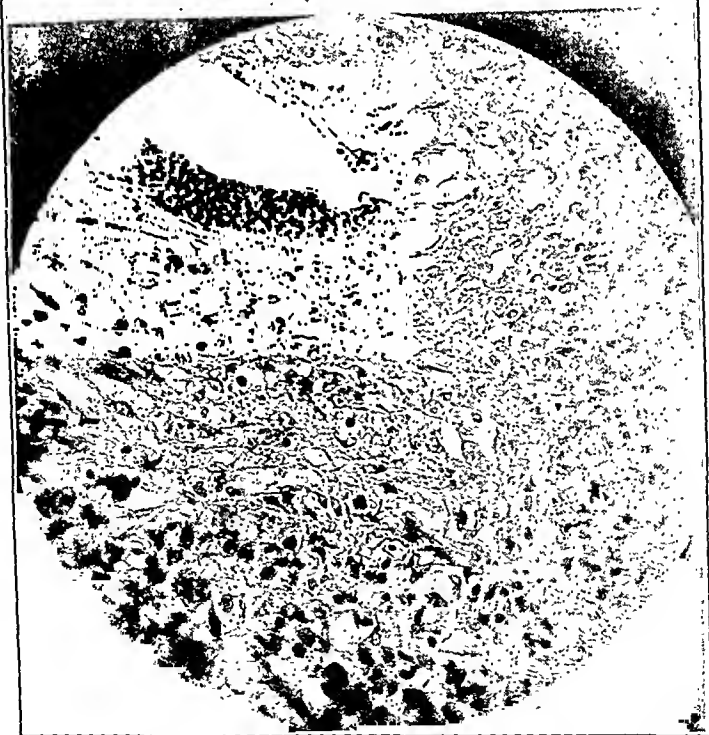


Fig. 3.—A low-power microscopic section of the tumor invading the adjacent wall of the pulmonary artery.

Fig. 4.—High-power microscopical section of the tumor, showing the polymorphous cellular pattern.

DISCUSSION

Strouse¹ has recently reported a case with a complete bibliography of primary tumors of the heart. For that reason we shall limit our references. His case report concerns a man who had symptoms of heart disease for forty-three years. The tumor, in keeping with the protracted history, was a benign myxoma of the right auricle. Strouse refers to the articles by Yater,² who gave a review of the literature in 1931, and Mead,³ who reported upon metastatic invasion from lung carcinoma in 1932. The general incidence of primary tumor of the heart is estimated at only 0.03 per cent, whereas metastatic growths give an incidence of 0.5 per cent. Since primary malignant tumors of the lungs or mediastinum may readily reach the heart, either through lymphatic drainage and venous return or by direct extension, it is not strange that most of such growths occur in the right side of the heart and, usually, the right auricle. The primary source might, however, be any portion of the body, with the possible exception of the brain, whence malignant tumors rarely metastasize. Few of these cardiac metastases produce symptoms; and if they do they are obscured by an excess of disturbances due to the primary growth. It is theoretically possible that both primary and secondary tumors may invade the conducting mechanism, or begin in the epicardium or pericardium and produce the signs (including the electrocardiographic) of pericarditis. Barnes, Beaver, and Snell,⁴ in 1934, reported the first case in which a primary malignant tumor was diagnosed ante mortem. They had the advantage of a deltoid muscle biopsy from an area of tenderness. This, coupled with the electrocardiographic proof of atrioventricular dissociation occurring acutely, led to the presumptive and correct diagnosis of a cardiac tumor. In Shelburne's case,⁵ reported in 1935, the correct diagnosis was likewise made ante mortem from pericardial evidence of a primary sarcoma of the pericardium, with electrocardiographic localization. Willius⁶ reported a fibrosarcoma of the right auricle in May, 1938. He gives a reference to Perlstein,⁷ who reported on sarcoma of the heart in 1918 and collected thirty cases of primary tumor, adding one of his own. Willius brings up the question of future possibilities of ante-mortem diagnosis and discusses certain electrocardiographic aids. Epicardial invasion, irritation, or fibrin accumulation, usually in association with pericarditis with effusion, yields reliable electrocardiographic diagnostic hints.

Boman⁸ has recently reported upon a primary sarcoma of the pericardium undiagnosed before death. He found Yater's classification of clinical types and their symptoms useful. Obviously, the pericardial irritation, fluid accumulation, and tendency to cardiac tamponade are more likely to induce obtrusive symptoms and physical signs than intramuscular or intra-cardiac protrusions.

Concerning the problem of making ante-mortem diagnoses of primary cardiac tumors, Strouse¹ makes the following logical comments: "It

must be admitted that practically all the information so far published has been based on *ex post facto* reasoning." However, this is the manner in which practically all improvements in diagnostic ability have been made. In retrospect, in our case, we feel that there was evidence sufficient, if it had been correlated, to at least lead to a presumptive diagnosis. Conditions that arise so rarely are likely to be totally out of mind. The following circumstances stand out conspicuously, and it may be worth while to group them in an attempt at summarizing such available data as might in later experience prove fruitful.

1. This patient did not have the usual history of any of the classical constitutional, congenital, or localizing cardiac lesions which commonly lead to congestive failure. Meroz,⁹ in his clinical report of three cases of primary tumor of the heart, strongly emphasizes this feature.

2. Her collapse was rapid and came without any suggestion of previous left ventricular strain. It was her first attack of congestive failure.

3. The right-sided heart failure, with such extreme overfilling of the veins and massive engorgement of the liver, without obvious, protracted ascites, dominated the picture. (Reference has already been made to the failure to secure the arm-to-tongue circulation time and a measurement of the venous pressure.) Acute cor pulmonale existed.

4. The lowering of the carbon-dioxide combining power of the plasma and the accompanying hyperpnea portray the compensatory efforts of the body to maintain homeostasis, or equilibrium.

5. Despite the evident need of oxygen she was not cyanotic, but had that murky hue which has been called "café au lait." She was not anemic enough to make visible cyanosis impossible on Lundsgaard's quantitative basis. Although there was an abundance of blood in the venous system, well oxygenated in the lungs, it was nevertheless unable to reach the systemic capillaries.

6. Had this tumor been of long duration, and had there been recurring attacks of congestive failure (see Strouse's report¹), the right ventricle should have been markedly hypertrophied. In that sense it might be well to consider right-sided heart obstruction as a whole. Blood fails to empty from the great veins into the right auricle in constrictive pericarditis. We have seen a large, metastatic, carcinomatous, fibrin-mixed plug grow into the mouth of the superior vena cava, gradually impeding flow from the inferior cava, as well. Theoretically, the tricuspid orifice could be blocked, but as an isolated phenomenon this does not occur. Blockage within the pulmonary arterial system (Ayerza's disease, pulmonary sclerosis and hypertension, etc.) produces prolongation of the circulation time, but the acute venous overfilling, as seen here, is not a feature.

The electrocardiogram, although it shows right axis deviation, does not indicate marked right ventricular preponderance. If there was a tumor plugging the right ventricular exit, and the heart was unable to accept

blood from the overfilled pulmonary veins, and if the evidence by ordinary physical methods, roentgenographic examination, and electrocardiographic tracings spoke against actual hypertrophy or thickening of the right ventricular wall, then it would logically be deduced that the tumor must be rapidly growing, and hence malignant.

7. The murmur at the base deserves analysis. With our patient's type of anemia, one of us (W. C. M.) felt that such a systolic murmur was neither uncommon nor determinative. In retrospect, however, the type of murmur, with increased venous pressure, and without any thrill, might well make one think of the possibility of pulmonary ostial obstruction that was of the diffuse, rather than the abrupt, type. This conclusion might be drawn from the fact that classical thrills are produced by obstructions which permit vibration and involve a limited opening, beyond which the stream enters an open space. This is exactly what did not obtain in this instance; therefore, a systolic murmur, without a thrill, occurring in a case of diffuse obstruction, might very well suggest that the stenosis is neoplastic in origin.

SUMMARY

We are reporting another instance of primary malignant tumor producing extreme diffuse stenosis of the pulmonary artery at its orifice. It was a polymorphous cell sarcoma. It invaded the wall of the pulmonary artery to, and beyond, its right and left branches. We have made brief reference to some of the available literature and have discussed some of the symptomatology and physical findings. Such an analysis may be of some assistance in the attempt to make ante-mortem diagnoses of this disease.

REFERENCES

1. Strouse, Solomon: Primary Benign Tumor of the Heart of Forty-Three Years' Duration, *Arch. Int. Med.* 62: 3, 401, 1938.
2. Yater, W. M.: Tumors of the Heart and Pericardium, *Arch. Int. Med.* 48: 627, 1931.
3. Mead, C. H.: Metastatic Carcinoma of the Heart, Secondary to Primary Carcinoma of the Lung, *J. Thoracic Surg.* 2: 87, 1932.
4. Barnes, A. B., Beaver, D. C., and Snell, A. M.: Primary Sarcoma of the Heart: Report of a Case With Electrocardiographic and Pathological Studies, *AM. HEART J.* 9: 480, 1934.
5. Shelburne, S. A.: Primary Tumors of the Heart, With Special Reference to Certain Features Which Led to a Logical and Correct Diagnosis Before Death, *Ann. Int. Med.* 9: 340, 1935.
6. Willius, F. A.: Clinic on Refractory Congestive Heart Failure of Relatively Short Duration; Comments; Postmortem Findings (Primary Fibrosarcoma of the Right Auricle), *Proc. Staff Meetings, Mayo Clinic* 13: 331, 1938.
7. Perlstein, I.: Sarcoma of the Heart, *Am. J. M. Sc.* 156: 214, 1918.
8. Boman, P. G.: Primary Sarcoma of the Pericardium; Report of a Case, *Ann. Int. Med.* 12: 258, 1938.
9. Meroz, E.: A Clinical Study of Three Cases of Primary Tumor of the Heart, *Internat. Clin.* 4: 331, 1917.

VENTRICULAR FIBRILLATION AS A CAUSE OF SUDDEN DEATH IN CORONARY ARTERY THROMBOSIS*

REPORT OF A CASE

F. JANNEY SMITH, M.D.

DETROIT, MICH.

THE dramatic occurrence of sudden death has been of intense interest for centuries. Post-mortem examinations, by different investigators, of persons dying suddenly and unexpectedly, have shown a large preponderance of cardiovascular lesions. In Hamman's¹ series, such abnormalities were present in 91 per cent; and of sudden deaths from heart failure, 65 per cent were due to affections of the coronary arteries. It is well known that in patients with coronary artery sclerosis sudden death may occur in those who have, or those who have not, had an actual occlusion and that in the cases of nonocclusion it is more frequent in patients who have had anginal pain. Levy² has shown, in an analysis of cases of sudden death from coronary disease, in 1933, that the occurrence of coronary thrombosis in patients with coronary artery sclerosis triples the probability of sudden death. In our own series of coronary thrombosis cases, of 80 patients known to be dead, twenty were reported to have died suddenly.

The cause of this abrupt termination of life in coronary artery thrombosis is rarely cardiac rupture. This lesion was present in only three of 762 autopsy cases of coronary artery disease in Levy's² series at the Presbyterian Hospital in New York City. The sudden fatality in the great majority of these patients with coronary artery disease is due to abrupt cessation of the heartbeat—ventricular asystole. Allbutt's³ theory of an overwhelming, sudden vagus stimulation, with paralysis of the pacemakers, causing cardiac standstill, has very little backing at the present time. The presumption exists that this sudden, unexpected death, both in patients with angina pectoris and those with coronary artery occlusion, is due to fibrillation of the ventricles. This presumption has developed in medical literature since Hoffa and Ludwig⁴ demonstrated, in 1850, that electrical stimulation of the mammalian heart led to ventricular fibrillation and death. In 1888, McWilliam⁵ propounded the theory of sudden death by ventricular fibrillation, a previously unrecognized form of failure of the heart's action in man. This view was fundamentally different from those entertained up to that time.

The strengthening of the opinion that ventricular fibrillation is the most frequent cause of sudden death in coronary artery disease rests chiefly upon a large amount of experimental and clinical data.

*From the Department of Medicine, Henry Ford Hospital.
Received for publication Dec. 1, 1938.

Ventricular fibrillation has been produced experimentally in the hearts of mammals by means of various electrical, thermal, mechanical, or chemical stimuli, or by the ligation of a main branch of a coronary artery. The arrhythmia outlasts the stimulation, and usually persists until the heart dies.

A striking similarity has been noted between the groups of symptoms associated with sudden death in patients with coronary disease and those attendant on ventricular fibrillation experimentally induced in animals.^{5, 6} Observers have noted in both instances the abrupt loss of consciousness, disappearance of the pulse, fall of blood pressure to zero, muscular relaxation occasionally preceded by brief rigidity or convulsive movements, congestion of the neck veins, pallor, cyanosis, a few deep or gasping respirations, dilatation of the pupils, followed by death of the animal or patient.

Lewis⁷ states that all forms of disordered heart action produced experimentally are known to occur clinically; and the reason that so few instances of ventricular fibrillation have been recorded in man is that the arrhythmia is, in all but the briefest instances, incompatible with life.

However, the recording of ventricular fibrillation in man has now been accomplished in numbers of instances, the great majority in persons whose death was expected and in whom the irregularity was recorded as a terminal development in the dying heart.⁸⁻¹⁵

Many examples of brief, transitory episodes of ventricular fibrillation have been recorded, as in the stage of ventricular standstill of Stokes-Adams seizures,¹⁶⁻²³ in the course of treating auricular fibrillation^{16, 24} with quinidin, or following carotid sinus pressure in a patient with auricular fibrillation.²⁶ Dock²⁶ has stated that in man ventricular fibrillation establishes and maintains itself with difficulty.

Both von Hoesslin¹³ and Penati²⁷ have recorded instances of ventricular fibrillation resulting in the sudden death of patients suffering from cardiac failure due to rheumatic heart disease; in both cases death followed an intravenous injection of strophanthin.

Published instances, however, of electrocardiographically recorded ventricular fibrillation causing sudden death in patients with known coronary disease are very few in number.

Hamilton and Robertson,²⁸ in 1933, obtained an electrocardiogram showing ventricular fibrillation in a patient during a fatal attack of angina pectoris. Autopsy showed sclerosis of both coronary arteries, but no occlusion or myocardial infarction. Meyer²⁹ took an electrocardiogram during a fatal attack of ventricular fibrillation in a patient who had previously had bundle branch block and evidence of myocardial disease. Calandre and Martin-Rodriguez,³⁰ and also M. Vela,³¹ secured an electrocardiogram showing ventricular fibrillation on a patient during a fatal attack of angina pectoris. No autopsy was done in either instance.

In order to add to the meager electrocardiographic data at the time of sudden cardiac death, we are reporting the following case, which is an instance of ventricular fibrillation and sudden death within the first few hours following coronary artery thrombosis. No other electrocardiographic record of ventricular fibrillation occurring during the period of active myocardial infarction following coronary artery thrombosis has been found in a review of the literature.

REPORT OF CASE

H. T. E., a man 40 years of age, a university instructor in an eastern city, had for three weeks been having frequent attacks of substernal pain on effort, accompanied by a numb sensation in his left arm. The attacks averaged about 5 to 10 minutes in duration and had been promptly relieved by nitroglycerine. He had been advised to drop his work and come to Detroit, where he had relatives, for a rest. On Dec. 14, 1937, at 7:00 A.M., he developed a continuous, heavy, substernal pain, which was not relieved by the usual dose of 1/150 grain of nitroglycerine. At 4:00 P.M., nine hours later, the pain continuing, he arrived at the hospital heart station, having just taken another tablet of nitroglycerine without relief. He was obviously ill. His face was pale and his forehead covered with beads of perspiration. The history quite clearly was that of coronary artery occlusion of nine hours' duration, and it was thought best to have him admitted to the hospital without taking time for physical examination, but since the electrocardiographic instrument was readily accessible, a tracing was made (Fig. 1).

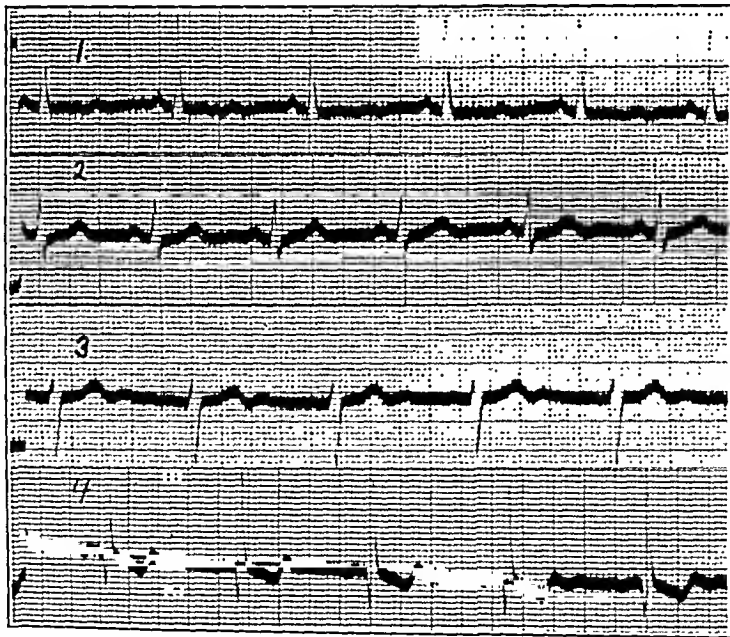


Fig. 1.—Electrocardiogram made nine hours after occlusion of the anterior descending branch of the left coronary artery, and five minutes before the development of ventricular fibrillation.

This electrocardiogram shows normal sinus rhythm, left ventricular preponderance, and diphasic T-waves in Lead I and Lead IV. Lead IV in this case was taken with the right arm electrode at the cardiac apex and the left arm electrode on the chest posteriorly.

As soon as this tracing had been completed the patient was given $\frac{1}{4}$ grain of morphine hypodermically. About three minutes later, while waiting for a wheel

chair to take him to his hospital room, he abruptly lost consciousness and gave a few irregular, clonic, convulsive movements. His pulse could not be palpated. Breathing was deep, irregular, and stertorous. The face was alternately pale, cyanotic, and congested. The pulsations in the neck were absent and the vessels became engorged. No heart sounds could be heard. The electrocardiographic electrodes were immediately reconnected, as soon as convulsive movements ceased, and while respiration was still occurring irregularly another electrocardiogram consisting of the standard three leads was recorded. At this time, very rapid, wide, diphasic oscillations of the string shadow were seen. During this recording respirations ceased except for an occasional gasp. The tracing taken at this time shows large, diphasic complexes of irregular height and frequency, occurring at a rate of 360, or more, per minute. The appearance of the tracing corresponds in every way to that of the previously published records of ventricular fibrillation in man and animals. In spite of the use of artificial respiration and the intracardiac injection of epinephrine, the patient was to all appearances dead following the completion of this tracing.

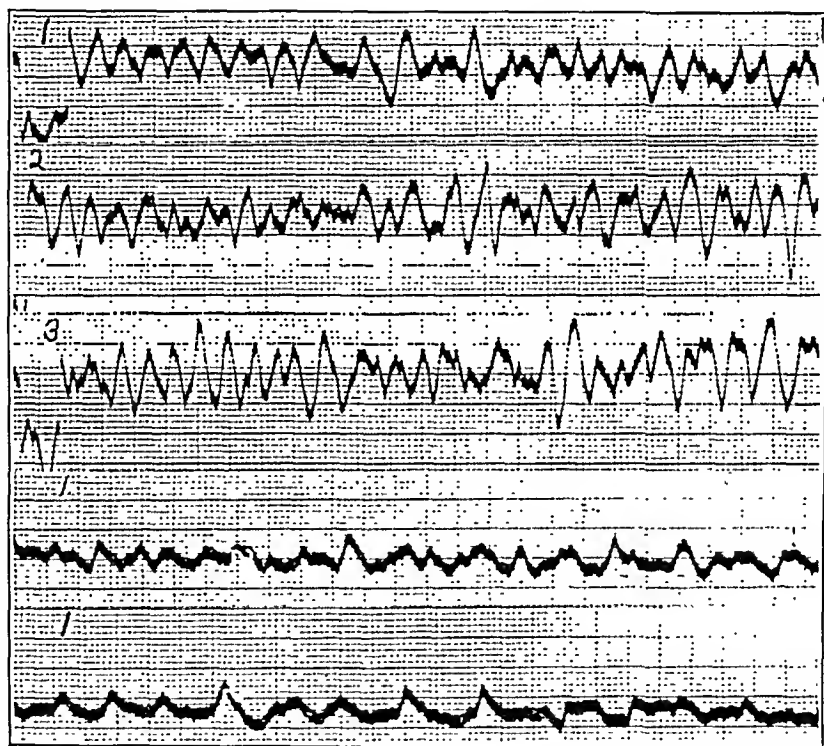


FIG. 2.—Electrocardiograms made immediately following a generalized convulsion. The first three tracings consist of the standard three leads and were made consecutively. The fourth and fifth are Lead I and were made at two-minute intervals.

About two minutes later another tracing was made from Lead I, and this was again repeated in two minutes (Fig. 2). Tracings were not continued beyond this point, so that we are not able to state how long the string movements continued. In the later tracings the amplitude of the oscillations was seen to be much smaller.

The autopsy was done by Dr. Penny. The cardiac findings alone were of interest. The myocardium of the left ventricle was softened over an area about 3.5 cm. in diameter, on the anterolateral surface, about 2.5 cm. above the tip. In this area, on section, the myocardium was mottled yellow in color. Elsewhere the myocardium of the left ventricle cut with increased resistance. Its wall averaged 1.3 cm. in thickness, and that of the right 0.7 cm. The coronary ostia

were patent, and the proximal aorta showed a few punctate atheromata. The anterior descending branch of the left coronary artery was extensively thickened and, in places, calcified from a point 1.5 cm. from the ostium to a point 3.0 cm. from the tip of the ventricle. At the proximal point of the thickening there was marked stenosis, and a small recent thrombus apparently completely occluded the lumen. The remainder of the artery was patent, but definitely stenosed and thickened. The left circumflex artery was also thickened and stenosed. The right coronary artery was dissected throughout and was markedly thickened by atheromatous plaques, but the lumen appeared adequate. The weight of the dissected heart was 390 grams.

Microscopic examination of the infarcted area in the left ventricle showed an early polymorphonuclear infiltration about the muscle fibers and slight haziness of their outlines, while a large amount of fibrosis was apparent in some areas (Fig. 3). Section through the thrombosed coronary artery showed marked thickening of the wall and an atheromatous nodule almost obliterating the vessel, leaving a tiny crescentic lumen to be plugged by the fresh thrombus.



Fig. 3.—Section through the thrombosed coronary artery, showing marked thickening of the wall and an atheromatous nodule almost obliterating the vessel, leaving a tiny crescentic lumen which was plugged by the fresh thrombus.

COMMENT

In this case ventricular fibrillation coincided with the sudden death of a patient who had had a thrombosis of the anterior descending branch of the left coronary artery and an early infarction of the anterior surface of the left ventricle. It is true that we were not fortunate enough

to record the transition from normal sinus rhythm to ventricular fibrillation, and hence are unable to state whether or not ventricular tachycardia or a period of cardiac standstill preceded this.

The first electrocardiogram, taken five minutes before death, deserves comment in that it showed no definite evidence of myocardial infarction, although, judging from the history, this had begun nine hours earlier, and autopsy disclosed that early infarctive alterations had definitely occurred. But, whereas with a sizable area of myocardial infarction characteristic electrocardiographic changes usually develop within the first few hours, it has occasionally happened that significant alterations did not appear until the following day.

In reviewing the treatment of the ventricular fibrillation in our patient and the other five with angina pectoris or coronary sclerosis it is apparent that it was entirely futile. In all but one patient adrenaline was injected into the heart, and, in two, cardiac massage was attempted.

The physiologists³² and cardiac surgeons^{33, 34} have made considerable strides in arresting experimentally produced ventricular fibrillation in animals by means of electric counter shock in combination with cardiac massage and the combined use of procaine hydrochloride, adrenaline, and calcium intravenously. Their work has been carried out, for the most part, on animals whose hearts were exposed by surgical incision.

The probability of being able to revive a patient with coronary occlusion from ventricular fibrillation by such means seems extremely remote.

SUMMARY

A case of coronary artery thrombosis is reported in which ventricular fibrillation, electrocardiographically recorded, caused sudden death.

REFERENCES

1. Hamman, L.: Sudden Death, *Bull. Johns Hopkins Hosp.* 55: 387, 1934.
2. Levy, R. L.: Sudden Death in Patients With Coronary Sclerosis and Thrombosis, *Tr. Am. Climat. & Clin. A.* 51: 85, 1935.
3. Allbutt, T. C.: *Diseases of the Arteries, Including Angina Pectoris*, London 2: 466, 1915, Macmillan & Co.
4. Hoffa, M., and Ludwig, C.: Einige neue Versuche ueber Herzbewegung, *Ztschr. f. rat. Med.* 9: 107, 1850.
5. McWilliam, J. A.: Fibrillar Contraction of the Heart, *J. Physiol.* 8: 296, 1887.
6. Hering, H. E.: *Der Sekundenherztod mit besonderer Berücksichtigung des Herzkammerflimmerns*, Berlin, 1917, J. Springer.
7. Lewis, Sir Thomas: *Diseases of the Heart*, New York, 1934, Macmillan & Co.
8. Robinson, G. C.: Study With the Electrocardiograph of the Mode of Death of the Human Heart, *J. Exper. Med.* 16: 291, 1912.
9. Halsey, R. H.: Case of Ventricular Fibrillation, *Heart* 6: 67, 1914-1915.
10. Dieuaide, F. R., and Davidson, E. C.: Terminal Cardiac Arrhythmias, *Arch. Int. Med.* 28: 663, 1921.
11. Schellong, F.: Elektrokardiographische Beobachtungen am sterbenden Menschen, *Ztschr. f. d. ges. exper. Med.* 36: 297, 1923.
12. Kahn, M. H., and Goldstein, I.: Human Dying Heart, *Am. J. M. Sc.* 168: 388, 1924.
13. von Hoesslin, H.: Der Herztod, nach elektrokardiographischen Aufnahmen, *Ergebn. d. inn. Med. u. Kinderh.* 39: 276, 1931.

14. Hanson, J. F., Purks, W. K., and Anderson, R. G.: Elektrocardiographic Studies of Dying Human Heart, With Observations on Intracardiac Injection of Epinephrine; Report of 25 Cases, *Arch. Int. Med.* 51: 965, 1933.
15. Sigler, L. H., Stein, I., and Nash, P. I.: Electrocardiographic Changes Occurring at Death, *Am. J. M. Sc.* 194: 356, 1937.
16. Kerr, W. J., and Bender, W. L.: Paroxysmal Ventricular Fibrillation With Cardiac Recovery in Case of Auricular Fibrillation and Complete Heart-Block While Under Quinidine Sulphate Therapy, *Heart* 9: 269, 1922.
17. Levine, S. A., and Matton, M.: Adams-Stokes Syndrome, Showing Ventricular Fibrillation and Asystole Lasting 5 Minutes, With Recovery Following Intra-Cardiac Injection of Adrenalin, *Heart* 12: 271, 1926.
18. de Boer, S.: Kammerflattern und Kammerflimmern bei einem Patienten mit totalem Herzblock, *Ztschr. f. d. ges. exper. Med.* 38: 191, 1923.
19. Gallavardin, L., and Bérard, A.: Possibilité d'une fibrillation ventriculaire transitoire avec accidents syncopaux analogues à ceux du Stokes-Adams et précédant la mort subite, *Arch. d. mal. du coeur* 20: 305, 1927.
20. Davis, D., and Sprague, H. B.: Ventricular Fibrillation; Its Relation to Heart-Block; Report of Case in Which Syncopal Attacks and Death Occurred in Course of Quinidine Therapy, *AM. HEART J.* 4: 559, 1929.
21. Schwartz, S. P.: Transient Ventricular Fibrillation; Study of Electrocardiograms Obtained From Patient With Auriculoventricular Dissociation and Recurrent Syncopal Attacks, *Arch. Int. Med.* 49: 282, 1932.
22. Freundlich, J.: Durch Kammerflattern ausgelöste Adams-Stokessche Anfälle, *Deutsches Arch. f. klin. Med.* 173: 617, 1932.
23. Bizzozero, R. C.: Fibrilación ventricular pasajera registrada durante una crisis sincopal en un síndrome de Stokes-Adams, *Rev. Argent. de cardiología* 1: 371, 1934.
24. Escamilla, R. F.: Report of Case of Paroxysmal Ventricular Fibrillation in Relation to Quinidine Therapy, *AM. HEART J.* 8: 850, 1933.
25. Shookhoff, C.: Ventricular Fibrillation With Cardiac Recovery, Caused by Carotid Sinus Pressure, in Case of Auricular Fibrillation, *AM. HEART J.* 6: 758, 1931.
26. Dock, W.: Transitory Ventricular Fibrillation as Cause of Syncope and Its Prevention by Quinidine Sulphate, With Case Report and Discussion of Diagnostic Criteria for Ventricular Fibrillation, *AM. HEART J.* 4: 709, 1929.
27. Penati, F.: Elektrokardiographischer Befund von Herzflimmern bei plötzlichem Herztod, *Klin. Wchnschr.* 12: 1249, 1933.
28. Hamilton, R. L., and Robertson, H.: Electrocardiographic Studies of Dying Heart in Angina Pectoris, *Canad. M. A. J.* 29: 122, 1933.
29. Meyer, P.: Mort subite par fibrillation ventriculaire au cours d'une myocardite chronique enregistrée à l'électrocardiographie, *Arch. d. mal. du coeur* 27: 1, 1934.
30. Calandre, L., and Martin-Rodriguez, F.: Muerte súbita por fibrilación ventricular, *An. de med. int.* 3: 483, 1934.
31. Vela, M.: Muerte súbita por fibrilación ventricular en un anginoso, *Arch. cardiología y hemat.* 17: 1, 1936.
32. Prevost, J. L., and Battelli, F.: Sur quelques effets des décharges électriques sur le coeur des mammifères, *Compt. rend. Acad. d. sc.* 129: 1267, 1899.
33. Hooker, D. R., Kouwenhoven, W. B., and Langworthy, O. R.: Effect of Alternating Electrical Currents on Heart, *Am. J. Physiol.* 103: 444, 1933.
34. Mautz, F. R.: Resuscitation of Heart From Ventricular Fibrillation With Drugs Combined With Electric Shock, *Proc. Soc. Exper. Biol. & Med.* 36: 634, 1937.

A SYNDROME OF EXOPHTHALMIC GOITER, ACUTE RHEUMATIC CARDITIS, AND HEART BLOCK*

CHAUNCEY C. MAHER, M.D., ALEXANDER SANDERS, M.D., SAMUEL G. PLICE, M.D., AND PAUL H. WOSIKA, M.D.

CHICAGO, ILL.

IN 1825, Parry¹ originally described a series of six cases of exophthalmic goiter. Rheumatic fever preceded the goitrous enlargement in one patient, and organic heart disease was present in two others. Basedow² (1840) described four cases of exophthalmic goiter; three of the patients had previously had rheumatic fever and valvular disease. Numerous reports have been made on the combination of exophthalmic goiter and rheumatic fever, notably, by Markham³ (1858), Garnier⁴ (1899), Froment⁵ (1906), Bouchut⁶ (1906), Coudray⁷ (1909), McCarrison⁸ (1917), Cabot⁹ (1929), and others.

Chronic rheumatic valvular disease is considered an occasional complication in exophthalmic goiter by White¹⁰ (1937). Yet Vincent¹¹ (1906) reported that of 156 cases of acute rheumatic fever, hyperthyroidism was a complication in 86. Conversely, Maher and Sittler¹² (1936) reported 180 cases of thyrotoxicosis, in 23.3 per cent of which rheumatic valvular involvement was present.

The occurrence of heart block and exophthalmic goiter has been reported frequently, among others, by Merklen¹³ (1882), Lewis¹⁴ (1913), Reilingh¹⁵ (1915), Dameshek¹⁶ (1924), Goodall and Rogers¹⁷ (1927), Simon¹⁸ (1927), Easton¹⁹ (1930), Cameron and Hill²⁰ (1932), Wedd²¹ (1932), Davis and Smith²² (1933), Carey²³ (1934), Kremer and Laplace²⁴ (1936), and Steuer²⁵ (1936).

A review of these reports shows a variation in opinion regarding the relationship of the heart block and the hyperthyroidism. Certain authors have suggested that the hyperthyroidism caused the block, but in cases in which autopsies were performed organic inflammatory lesions usually were found.

The authors have observed a number of patients with typical exophthalmic goiter associated with acute carditis. Of this group, four whose records are complete will be reported in detail. The patients were observed during thyroidectomy and from six months to four years thereafter.

REPORT OF CASES

CASE 1.—E. S. was a 20-year-old, white, unmarried, shipping clerk. His family history was recorded as negative for goiter, rheumatism, and heart disease. As a child, he frequently developed sore throats, so that tonsillectomy and adenoidectomy were performed at 11 years of age. At 14 years of age, acute rheumatic fever developed. At 18, he was subjected to a resection of the nasal septum.

*From the Department of Medicine, Cook County Hospital, Chicago, Ill.

Received for publication Dec. 7, 1938.

Examination of the patient in the Cook County Hospital revealed the typical findings of exophthalmic goiter, with a basal metabolic rate of plus 50 to plus 55 per cent. The cardiac findings were characteristic of mitral stenosis and insufficiency.

The first electrocardiogram showed a prolonged P-R interval with fusion of the P and T waves. Serial electrocardiograms taken during the following weeks showed various types of block, including Wenckebach periods, occasional dropped beats, 2:1 ratio, and complete auriculoventricular block. The temperature tended to be slightly elevated, ranging from 98° F. to 100° F., and there was a leucocytosis which did not exceed 14,200. He complained occasionally of sore throat and had a few nosebleeds. There was mild joint distress, but no objective manifestations of arthritis were present.

The administration of iodides was effective in lowering the basal metabolic rate to plus 17 per cent, and subtotal thyroidectomy was accomplished without incident.

Examination three weeks after operation showed no change in the murmurs; and no difference in the size and shape of the heart roentgenographically; the electrocardiogram showed a normal P-R interval. The basal metabolic rate was normal. The patient returned to work and three years later showed no evidence of hyperthyroidism, but the same valvular defects persisted.

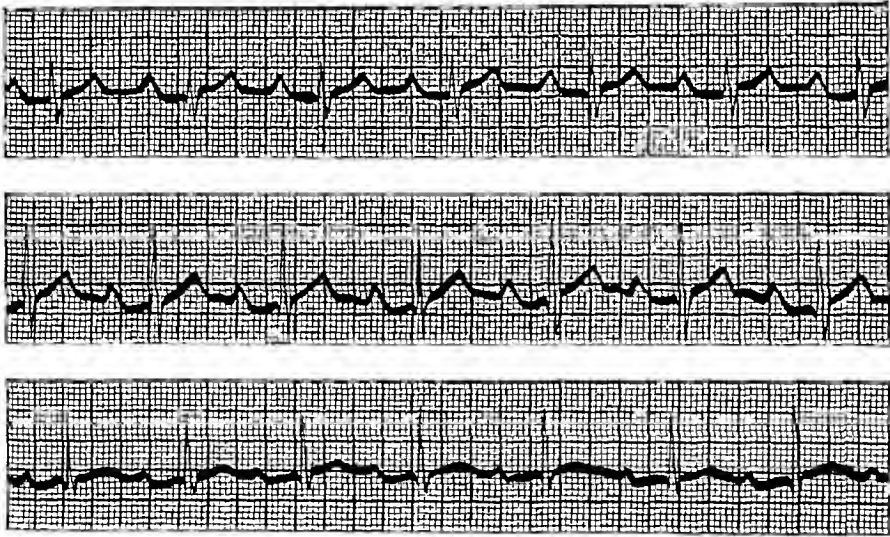


Fig. 1.—Electrocardiogram in Case 1 (E. S.), from a series showing partial auriculoventricular heart block with prolonged P-R interval.

CASE 2.—J. P. was an unmarried, white laborer. His family history was recorded as negative for goiter, rheumatism, and heart disease. At 15 years of age, he developed vague backaches which lasted for a period of two months. On entrance into the Cook County Hospital he presented the typical findings of exophthalmic goiter, with a basal metabolic rate of plus 35 per cent. He was suspected of having aortic valvulitis because of an aortic systolic murmur.

Soon after admission the patient developed acute pharyngitis, with a rise of temperature to 103° F., a leucocytosis of 12,000, and marked prostration. Joint manifestations were mild. Serial electrocardiograms showed a variable prolongation of the P-R interval, dropped beats, and complete A-V block. The variable heart block persisted throughout a two-month period and never was discovered again, though frequent electrocardiograms were taken. The basal metabolic rate rose rapidly to plus 85 per cent, and remained above plus 65 per cent for several months. During this time definite findings of aortic stenosis, and, later, mitral stenosis, appeared, with increase in size of the heart and change in its shape in the roent-

genogram. In this same period, rest in bed, sedatives, large and small doses of Lugol's solution, and roentgenotherapy failed to reduce his basal metabolism substantially or improve his condition generally. Finally, hemithyroidectomy was performed, and, later, the remainder of the gland was removed.

This patient was followed for a period of three years after thyroidectomy. The metabolic level remained normal. He still presented the findings of mitral and aortic valvular disease.

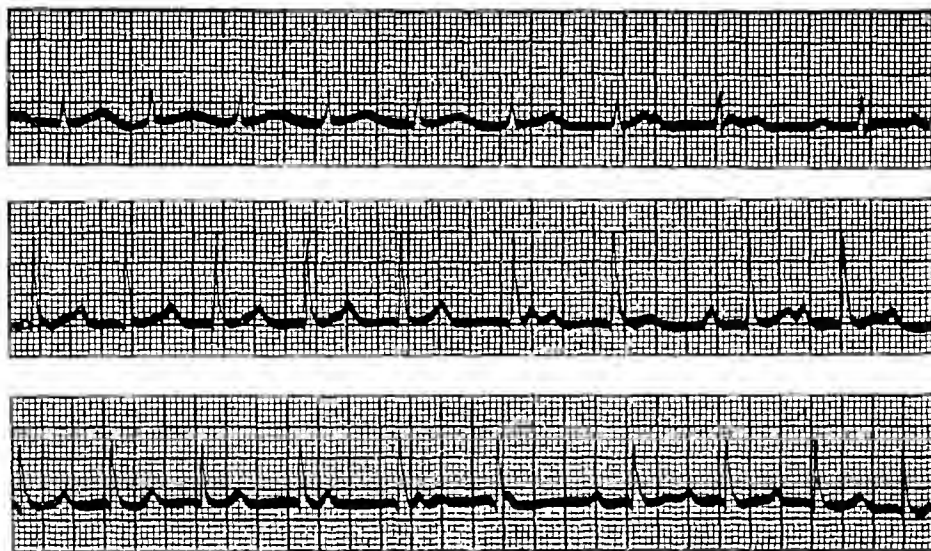


Fig. 2.—Electrocardiogram in Case 2 (J. P.), from a series showing partial auriculoventricular heart block with Wenckebach periods.

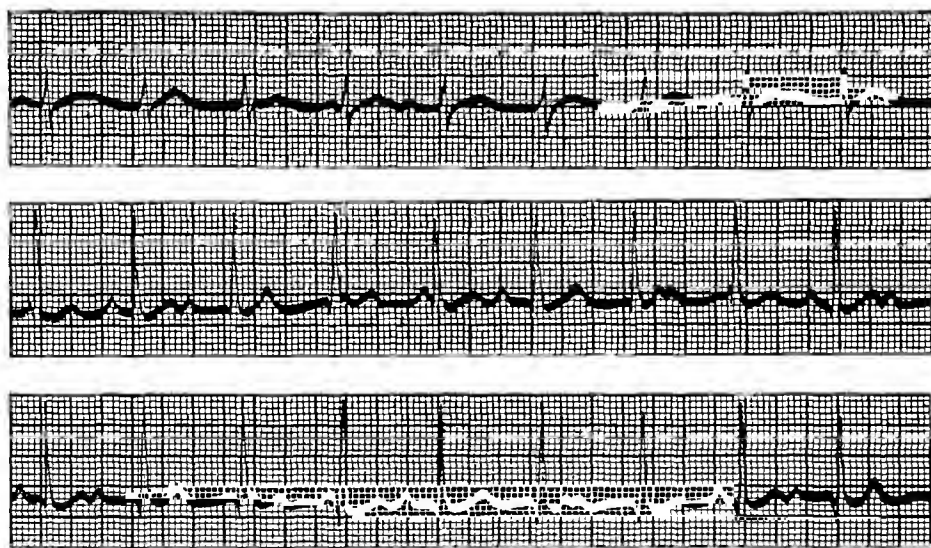


Fig. 3.—Electrocardiogram in Case 2 (J. P.), from a series showing complete auriculoventricular heart block.

CASE 3.—A. M. was a white, unmarried cook, 22 years of age. His family history was significant from the standpoint of rheumatism, as two sisters had had rheumatic fever and one of them had succumbed to rheumatic heart disease. When 4 years old the patient developed acute rheumatic fever, after frequent attacks of acute upper respiratory infections. When he was 7 years old a tonsillectomy was performed. On entrance to the Cook County Hospital he presented the typical picture of exophthalmic goiter, with a basal metabolic rate of plus 30 per cent. He

had mitral stenosis and insufficiency. One electrocardiogram showed a P-R interval of 0.28 sec. After the administration of iodides his basal metabolic rate dropped to plus 14 per cent, and subtotal thyroidectomy was performed.

This patient was readmitted to the hospital on our service two years later. At this time he showed no clinical evidence of hyperthyroidism, and had a basal metabolic rate of plus 4 per cent. He showed the characteristic findings of mitral stenosis. The electrocardiogram showed prolongation of the P-R interval with occasional dropped beats. Frequent electrocardiograms showed that the degree of block was variable and the P-R interval occasionally normal.

Four years afterward, the patient was observed when he contracted a primary syphilitic lesion followed by a secondary rash. The cardiac findings were those of mitral stenosis and insufficiency, with prolongation of the P-R interval and occasional dropped beats.

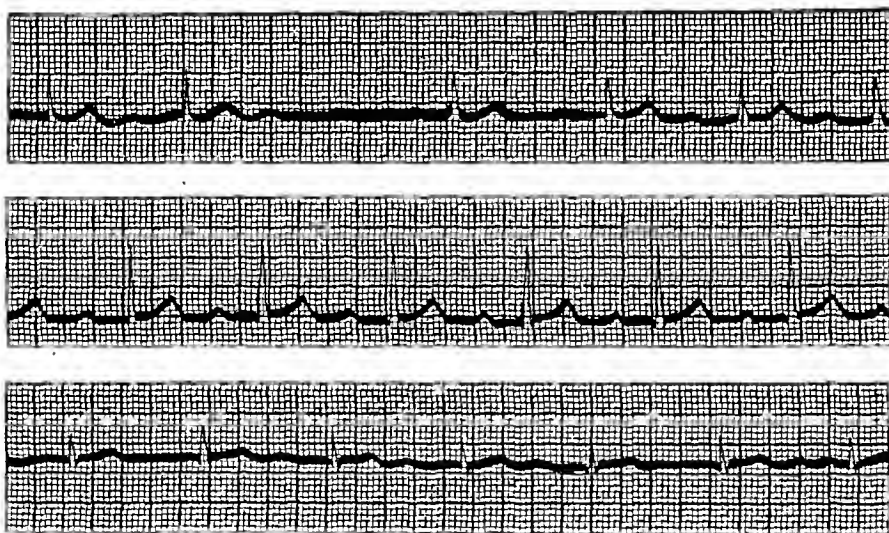


Fig. 4.—Electrocardiogram in Case 3 (A. M.), from a series showing partial auriculo-ventricular heart block with prolonged P-R intervals and dropped beats.

CASE 4.—L. P. was a white, unmarried waiter, 28 years of age. His family history was negative for goiter, rheumatic fever, and heart disease. When 19 years old he contracted typhoid fever. He developed acute rheumatic fever when he was 21. On entrance into the Cook County Hospital he presented the typical picture of exophthalmic goiter (basal metabolic rate, plus 55 per cent). The cardiac findings were characteristic of mitral stenosis. On admission the patient had pharyngitis, with prostration and vague joint distress, but no redness or swelling of the joints. The temperature range was from 98.2° F. to 101.4° F. The pulse rate was 100 to 140 per minute. The leucocyte count was 23,200. Electrocardiograms showed a first degree block (P-R interval, 0.24 sec.) which persisted for two weeks. After one month of iodine therapy, the basal metabolic rate was lowered to plus 16 per cent and thyroidectomy was performed.

This patient was followed for a period of one month after thyroidectomy. The basal metabolic rate remained normal. He still presented the findings of valvular heart disease.

DISCUSSION

In reviewing the literature one is able to find a number of case reports of heart block as a complication of hyperthyroidism. The majority of opinions appear to be against considering the thyroid intox-

iation as a causative factor in the production of the block. Infection has been suggested frequently as a probable cause and has been found in some cases at autopsy. Further review shows that rheumatic heart disease may also complicate hyperthyroidism. The possibility, however, that the heart block complicating hyperthyroidism may be due to acute rheumatic carditis has not been proved, although it is recognized that one of the most common causes of transient heart block (excluding digitalis) is acute rheumatic infection. The patients in this report illustrate this relationship.

All of these patients presented the classical picture of exophthalmic goiter. They had exophthalmos, diffusely enlarged thyroid glands with an audible bruit, tremor of the hands, and emotional instability. In all of them the basal metabolic rates were elevated abnormally. After thyroidectomy the symptoms of hyperthyroidism subsided, and the basal metabolic rates returned to normal and remained so.

They all presented evidence of valvular heart disease, three with mitral lesions and one with aortic and mitral involvement. The best evidence for active cardiac infection was the actual development of valvular disease in Case 2. Other evidence was the occurrence of sore throats, leucocytosis, slight fever, and joint pains.

The occurrence of heart block, when correlated with the complete clinical picture, constitutes further evidence of active rheumatic carditis. None of these patients received digitalis in any form. The actual explanation of the sequence of events depends upon an analysis of many cases of many types, each contributing corroborating evidence.

It would appear that hyperthyroidism may develop at any time in the course of a rheumatic cardiac syndrome. In Cases 1 and 4, in which there had been a childhood rheumatic infection, the onset of hyperthyroidism appeared to coincide with an exacerbation of the rheumatic carditis. In Case 2 the rheumatic and hyperthyroid syndromes seemed to have begun at about the same time. In other patients not included in this series, hyperthyroidism developed long after the acute rheumatic carditis subsided.

The heart block appears to be dependent upon the rheumatic infection and unrelated to the hyperthyroidism. Thus, in Case 2, the block disappeared two months after the onset of the pharyngitis and never reappeared, even though the hyperthyroidism persisted six months longer. In Case 3, block was present before operation during active hyperthyroidism and was known to have persisted four years after operation in varying degrees, presumably changing with the rheumatic state. In Case 4, the heart block stopped before thyroidectomy was performed, and in Case 1 the block disappeared after the operation. The absence of correlation between the cessation of the block and the termination of the hyperthyroid state would seem to sustain the contention that the heart block is not caused by the hyperthyroidism. The

course and variability of the heart block are similar in rheumatic carditis without the complicating element of hyperthyroidism. It may well be reiterated that the diagnosis of the heart block can be made definite only by electrocardiographic examination. Routine stethoscopic examinations will seldom disclose minor degrees of block. It has been found that serial electrocardiograms are necessary to detect this complication.

Observation of these patients over a long period permits the conclusion that the hyperthyroidism is a transient episode in the course of rheumatic heart disease, with heart block as a complication at that particular time. It would appear that infections, particularly of the rheumatic type, exert an unfavorable influence upon the hyperthyroidism. Apparently, however, the hyperthyroid state does not appreciably aggravate the cardiac infection. The temperature curves were comparatively low. The general condition was better than might be expected in the average rheumatic patient. In the four patients reported the manifestations of the disease in the joints were mild. In other patients, marked swelling and redness of the joints have been observed, and two patients have developed erythema nodosum.

SUMMARY

1. Four cases of exophthalmic goiter, acute rheumatic carditis, and heart block have been observed and reported.
2. It would appear that the hyperthyroidism is an episode in the course of the rheumatic heart disease, with heart block as an incidental complication.
3. Active infection of the rheumatic type seems to increase the severity of the hyperthyroidism.
4. The hyperthyroidism, conversely, apparently enables the patient to withstand the rheumatic infection better.
5. In exophthalmic goiter, heart block as a manifestation of acute carditis will be found more frequently if serial electrocardiograms are taken.

REFERENCES

1. Parry, C. H.: *Collected Works* 1: 478, London, 1825.
2. Basedow, C. A.: *Exophthalmos durch Hypertrophie des Zellgewebes in der Augenhöhle*, *Wehnschr. f. d. ges. Heilk.* 6: 197, 1840.
3. Markham, Dr.: *Affection of the Heart With Enlargement of the Thyroid and Thymus Glands and Prominence of the Eyes*, *Tr. Path. Soc. London* 9: 163, 1858.
4. Garnier, M.: *La Glande Thyroïde dans les Maladies Infectieuses*, Paris, 1899.
5. Froment, J.: *Cardiopathies Valvulaires Compiquées de Basedowisme*, Lyons, 1906.
6. Bouchut, L.: *Rôle du Rhumatisme Articulaire Aigu et Subaigu dans L'Étiologie de la Maladie de Basedow et dans sa Terminaison par L'Asystolie*, Lyons, 1906.
7. Coudray, P.: *De L'Influence des Maladies Infectieuses sur la Glande Thyroïde*, Montpellier, 1909.
8. McCarrison, R.: *The Thyroid Gland in Health and Disease*, New York, 1917, William Wood and Company.

9. Cabot's Case Record, No. 15472: Exophthalmic Goiter and Acute Rheumatic Fever, *New England J. Med.* 201: 1056, 1929.
10. White, P. D.: *Heart Disease*, New York, 1937, p. 303, The Macmillan Company.
11. Vincent: Signe Thyroïden dans le Rheumatisme Articulaire Aigu, *Société médicale des hôpitaux de Paris*, June 8, 1906.
12. Maher, C. C., and Sittler, W. W.: The Cardiovascular State in Thyrotoxicosis, *J. A. M. A.* 106: 1546, 1936.
13. Merklen: Accidents Aigus dans le Cours d'un Goitre Exophthalmique Datant de Six Ans: Fièvre, Diarrhee, Hyperasthésie Générale, Intermittences Prolongées du Coeur Suivies d'accès Épileptiformes: Guérison des Phénomènes Aigus, *Bull. Soc. Clin. de Paris* 5: 53, 1882.
14. Lewis, T.: Certain Physical Signs of Myocardial Involvement, *Brit. M. J.* 1: 484, 1913.
15. de Vries Reilingh, D.: Een Zeldzame Stoornis in de Hartwerkzaamheid bij Morbus Basedow, *Nederl. tijdschr. v. geneesk.* 2: 1425, 1915.
16. Dameshek, W.: The Heart in Hyperthyroidism, *Boston M. and S. J.* 190: 487, 1924.
17. Goodall, J. A., and Rogers, L.: The Electrical and Histological Manifestations of Thyrotoxic Myocarditis, *Brit. M. J.* 1: 1141, 1927.
18. Simon, E.: Über Herzblock nach Kropfoperationen, *Zentralbl. f. Chir.* 54: 2060, 1927.
19. Easton, J.: Toxic Goiter and Some Complications, *Tr. Med. Chir. Soc. Edinburgh*, p. 54, 1929-1930; *Edinburgh M. J.* 37: 54, 1930.
20. Cameron, J. D. S., and Hill, I. G. W.: Heart Block in Toxic Goiter, *Edinburgh M. J.* 39: 37, 1932.
21. Wedd, A. M.: Complete Heart Block, Auricular Fibrillation and Abnormal Ventricular Complexes in a Case of Acute Rheumatic Fever, *Clifton M. Bull.* 18: 63, 1932.
22. Davis, A. C., and Smith, H. L.: Complete Heart Block in Hyperthyroidism Following Acute Infections: A Report of Six Cases With Necropsy Findings in One Case, *AM. HEART J.* 9: 81, 1933.
23. Carey, T. N.: Complete Heart Block Following Thyroidectomy; Autopsy Evidence of Rheumatic Carditis, *Bull. School Med. Univ. Maryland* 19: 8, 1934.
24. Kremer, D. N., and Laplace, L. B.: Heart Block Following X-Ray Treatment for Thyrotoxicosis, *AM. HEART J.* 11: 227, 1936.
25. Steuer, L. G.: Complete Heart Block in Hyperthyroidism, *AM. HEART J.* 11: 623, 1936.

In Memoriam

LOUIS GROSS

1895-1937

Louis Gross was born in Montreal, Canada, on May 5, 1895. He entered the Medical School of McGill University in September, 1911, after graduation from the Montreal High School. During the course in medicine he won honors for extra-curricular studies and led his class in the aggregate for the five years, for which he received the Holmes Gold Medal, the highest honor which can be won by an undergraduate in medicine at McGill University.



Louis Gross

He decided at once upon an academic career, with research as the main object. As Douglas Fellow in Pathology, he spent the next five years in the Department of Pathology at the Medical School of McGill University, under the direction of Professor Horst Oertel. The major part of his time was devoted to research on the circulation of kidneys and heart. The monograph which he published in 1921 on the Blood Supply to the Heart is a classic, and will remain always as a monument to the industry and unusual ability of this remarkable young man.

Versatility was an outstanding characteristic of Louis Gross, and even in this respect he was unusual, because he excelled in everything he undertook to learn or do. As a musician and artist he was superior

to the average amateur and would have been successful as a professional had he chosen either of these fields as a career. His ingenuity and natural inventive ability helped him greatly in his later work. He was given a scholarship to induce him to continue his study of sculpture abroad, but it did not tempt him to abandon medicine. He did go abroad, but to do medical research and to broaden his basic knowledge of medicine. From 1921 to 1923, he was in London, England, first with Sir Arthur Keith, at the Royal College of Surgeons, and then, as a Beit Memorial Fellow, at University College, where he completed a valuable study on the effect of vitamin B₁ deficiency on the movements of the rat's intestine in vivo and in vitro. To acquire more knowledge of bacteriology, he spent the next year in the research department of the Board of Health under the direction of Dr. William H. Parke. After a short period as Director of Laboratories at the Brownsville and East New York Hospital, he became, in 1925, Associate Pathologist at Mount Sinai Hospital, in New York. In 1928, at the age of thirty-two years, he was appointed Director of Laboratories at Mount Sinai Hospital, in New York, with which institution he remained associated, in this position, until his death.

Although his administrative duties were heavy, yet he managed to find time almost every day for the pursuit of his own researches. Until about three years before his death, his work involved mainly the application of his knowledge of morbid morphology and of bacteriology. His contributions to our knowledge of rheumatic heart disease and coronary disease will remain permanent milestones in the history of these subjects. In recent years he began to apply experimental methods to his study of myocardial disease and of diseases of the circulatory system in general. His remarkable ingenuity asserted itself, and at once his work bore fruit. In 1937 he received medals from the American Medical Association and from the Canadian Medical Association when he demonstrated the results of what he considered only preliminary studies. Contributions of the greatest value to this field of medicine were undoubtedly prevented by his tragic and untimely death on Oct. 17, 1937. He was an outstanding student, an honest, careful, critical investigator, a great teacher, and a stimulating, brilliant lecturer.

I realize that no one who has read so far and who did not know Louis Gross can possibly have a proper conception of this extraordinary person. Although much absorbed in his own work, yet he was greatly interested in young men who were planning a career in medicine, particularly in research, and he played a most important part in the life of many young doctors. In his laboratory he made room for many young men to do part-time research, always a great burden to the administrator of a large department. He was sternly critical of the results obtained by these men, and did not permit publication of any study which, in his opinion, would not stand the test of time. The high quality of the

publications which appeared during his tenure of office is directly attributable to him. Above all else he was a warm-hearted, devoted, sincere friend to all whom he considered worthy of his friendship.

His associates and collaborators learned much from him and greatly enjoyed working with him. His aim was always the truth and not the credit. The matter of credit, especially for himself, was always of secondary importance to credit to the Institution and to his associates. The smallest contribution to a study by a part-time worker was always given full and frequently disproportionate recognition. He was an indefatigable worker, derived much pleasure from his work, and had such a buoyant, cheerful disposition that to collaborate with him was an enjoyable experience. He gave freely and generously of himself to those whom he trusted, admired, and loved, and he left behind him a host of dear friends who mourn his loss and in whose memory he will remain until their own death.

Harry Goldblatt.

Department of Reviews and Abstracts

Selected Abstracts

Grossman, Edward B., and Williams, John R.: Relation of Age to Renal Pressor Substance. *Arch. Int. Med.* 62: 799, 1938.

Injection of extracts containing renal pressor substance (renin) into rats of various ages showed the least rise in blood pressure in the youngest rats and the greatest rise in the oldest. On the other hand, the youngest rats had the most pressor substance in their own kidneys, and the oldest rats had the least.

The experiments suggest a possible relation between the increased sensitivity of senile rats to renal pressor substance and the tendency of elderly persons to show hypertension. However, it is concluded that no convincing evidence of such a relation exists at present.

NAIDE.

Fatherree, Thomas J., and Allen, Edgar V.: Sympathetic Vasodilator Fibers in the Upper and Lower Extremities: Observations Concerning the Mechanism of Indirect Vasodilatation Induced by Heat. *Arch. Int. Med.* 62: 1015, 1938.

The mechanism of indirect vasodilatation was investigated, and experiments were carried out to determine the presence of sympathetic vasodilator nerves in the upper and lower extremities of man.

It was shown that indirect vasodilatation induced by warming an extremity depends on the return of the blood from the warmed extremity to the general circulation. It was shown further that the occurrence of indirect vasodilatation in a digit depends on the integrity of its sympathetic nerve supply.

Evidence was obtained in favor of the view that there are sympathetic vasodilator nerves in the upper and lower extremities in man.

AUTHORS.

Boylston, G. A., McEwen, E. G., and Ivy, A. C.: A Pressor Substance Is Not Present in the Perfusate of Ischemic Kidneys. *Proc. Soc. Exper. Biol. and Med.* 39: 559, 1938.

Experiments have been carried out to determine whether or not the perfusate of ischemic kidneys of hypertensive dogs contains a pressor substance in significant amounts. Hypertension was produced in dogs by unilateral constriction of the renal artery and explanting the kidney into the flank. In one group of dogs after four days the explanted kidney was removed and perfused with warm Locke's solution for from twenty to sixty minutes. Dogs were used as assay animals. The perfusate was injected into the femoral vein of the anesthetized assay animals and systolic and diastolic blood pressures were determined in the unanesthetized state with the Hamilton recording optical manometer. In a second group of dogs, the same procedure was carried out after frank hypertension had persisted for at least three months. From these experiments there was no evidence of a pressor substance in significant amounts from the ischemic kidneys of the hypertensive dogs.

HINES.

Pickering, G. W., and Prinzmetal, M.: *Experimental Hypertension of Renal Origin in the Rabbit*. Clin. Sc. 3: 357, 1938.

A simple method is described of making clamps of known size suitable for constricting the renal artery in the rabbit.

In the rabbit, constriction of one renal artery, the other kidney being intact, is sometimes followed by a small and transient rise of blood pressure, and usually by atrophy of the ischemic kidney.

Constriction, by suitable clamps, of both renal arteries or of the renal artery to the only functioning kidney is followed by a slow rise of arterial pressure to a level which may be nearly double the preoperative value. In such animals with hypertension, the heart is hypertrophied and the degree of hypertrophy seems to be related, though not closely, to the degree of hypertension.

AUTHORS.

Zeus, L.: *Experimental Influences of Thyrotropic Hormone on the Heart*. Arch. f. Kreislauf. 4: 49, 1939.

The author demonstrated a dilatation of the heart, especially the right, following thyrotropic hormone administration. This occurred in four rabbits following daily injection of 200 ME. Histologically, the changes resembled those seen with thyroxin. These consisted of an increase in connective tissue, histiocytic cell infiltration, and cloudy swelling and fatty degeneration, especially in the right ventricle. This dilatation is followed after some days by hypertrophy. The hypertrophy is predominantly in the right ventricle.

KATZ.

Hollmann, W., and Guckes, E.: *The Triogram and Its Clinical Significance*. Arch. f. Kreislauf. 4: 69, 1939.

A systematic description is given of the stereotriogram and triogram in various clinical conditions such as axis shift, preponderant hypertrophy, extrasystoles, and intraventricular block. The practical value of this method demands more intensive study.

KATZ.

Müller, A.: *The Mechanics of Flowing Streams With Comments on Hemodynamics. II. Flow in Tubes. Part I. Reynolds' or Turbulent Flow*. Arch. f. Kreislauf. 4: 105, 1939.

This is an excellent detailed mathematical treatment of the subject, including investigations by the author. The author demonstrates that the pressure gradient in turbulent flow is about three times as great as with laminary nonturbulent flow. The profile of velocity across the cross section of a tube is the same in turbulent as in nonturbulent flow. Other details cannot be briefly abstracted but require examination of the original article.

KATZ.

Maegraith, B. G., and Carleton, H. M.: *Aortic Arteriosclerosis in Rabbits*. J. Path. and Bact. 48: 33, 1939.

Forty-five of 144 rabbits examined exhibited macroscopic changes in the aorta. These animals had been used for many different kinds of experiments, some of which were designed to raise the systemic blood pressure. Thirty-eight animals had heightened arterial pressure and of these, fourteen exhibited arteriosclerosis. This incidence of arterial lesions is of the same order as that found in the other animals examined, namely thirty-one out of 106.

The type of lesion observed is essentially medial and resembles the changes described by certain authors resulting from excision of the carotid sinuses, the injection of adrenalin.

From these observations it would seem that the rabbit is unsuitable for experimental work on the production of arterial disease. The high incidence of aortic lesions in our rabbits suggests, however, that the rabbit community might be useful for the investigation of the origin of spontaneous arteriosclerosis.

AUTHORS.

Essex, Hiram E., Herrick, J. F., Baldes, Edward J., and Mann, Frank C.: Influence of Exercise on Blood Pressure, Pulse Rate and Coronary Blood Flow of the Dog. *Am. J. Physiol.* 125: 614, 1939.

A series of experiments has been done on control dogs and dogs in which thermostromuhr units had been previously applied to the coronary arteries in an effort to determine the effect of exercise on the pulse rate, blood pressure, and coronary blood flow. Each animal had been accustomed to perform work at different rates on a treadmill.

Preliminary experiments demonstrated that the presence of the coronary thermostromuhr unit had no significant effect on the electrocardiograms or blood pressure of the animals studied.

Successive increases in the rate of work produced additional rises in blood pressure which were roughly proportional to the rate of work for the individual animals in both the control and experimental groups. As a given rate of work continued, the behavior of the blood pressure varied from animal to animal. In certain experiments the blood pressure reached a maximal level early and declined; in some it remained near the maximum; while in others it continued to augment throughout the period of exercise.

The pulse rate of the dog is a less reliable index of the rate of work than the blood pressure. The maximal pulse rate with low rates of work may be as great initially as with higher rates of work.

Simultaneous records of pulse rate, blood pressure, and coronary blood flow were made during exercise. The marked increases and decreases of coronary blood flow observed with various increments and decrements of work could not be satisfactorily accounted for by changes in blood pressure alone. The change in pulse rate with exercise was usually a better criterion than the blood pressure of changes in coronary blood flow. The evidence indicates other influences as important as blood pressure in augmenting coronary blood flow when a trained dog is given successive increments in the rate of work.

AUTHORS.

Chen, K. K., Robbins, E. Brown, and Worth, Harold: The Significance of Sugar Component in the Molecule of Cardiac Glycosides. *J. Am. Pharm. A.* 27: 189, 1938.

The potency of five cardiac aglycones—strophanthidin, digoxigenin, digitoxigenin, calotropagenin and seillaridin A—has been carefully determined.

Each aglycone is less powerful on the heart than its parent glycoside, more pronounced in frogs than in cats. If the aglycone undergoes chemical changes during hydrolysis, as in the case of seillaridin A and calotropagenin, the cardiac action is reduced much further.

The emetic action of strophanthidin, digoxigenin, and digitoxigenin, on the other hand, is greater than that of cymarín, digoxin, and digitoxin, respectively, molecule for molecule. When the structure of the aglycone is modified during hydrolysis, such as calotropagenin, the emetic action is diminished, but not to the same extent as the cardiac action.

The persistence of action among the aglycones is slight; that is, they are all rapidly eliminated from the circulation. This is particularly true with digitoxigenin in contrast with digitoxin.

Digitoxigenin caused a brief initial stimulation as manifested by convulsions, followed by marked depression of the central nervous system in cats and frogs. Digitoxin has no such action in corresponding doses.

AUTHORS.

Kienle, F.: Clinical and Electrocardiographic Observations on Traumatic Posterior Wall Infarct. *Ztschr. f. Kreislaufforsch.* 30: 674, 1938.

An injured skier came to the clinic with severe cardiac insufficiency, and clinical evidence supported by the roentgen and electrocardiographic examination indicated myocardial infarction.

KATZ.

Staemmler, M.: Does a Primary Hypertension of the Lesser Circuit Exist? (So-called Primary Pulmonary Sclerosis.) *Arch. f. Kreislaufforsch.* 3: 125, 1938.

The various anatomic forms of primary pulmonary sclerosis are considered to be the result of a primary hypertension of the arterioles of the pulmonary circulation. The first change is hypertrophy of the media of the arterioles and elastica of the medium sized arteries. The other anatomic changes are secondary.

KATZ.

Kunkel, Paul, Stead, Eugene A., Jr., and Weiss, Soma: Blood Flow and Vasomotor Reactions in the Hand, Forearm, Foot, and Calf in Response to Physical and Chemical Stimuli. *J. Clin. Investigation* 18: 225, 1939.

Following strong sensory stimuli, such as pinching the skin until pain is caused, or a sudden, loud noise, the forearm and calf respond in three ways: (1) by a decrease in volume after a latent period of from 3 to 9 seconds; (2) by an increase in volume after a latent period usually not exceeding 2 seconds; (3) by a biphasic response with first an increase in volume with a short latent period usually not exceeding 2 seconds, and subsequently a decrease in volume.

Reasons are stated for the belief that the decrease in volume is the result of active reflex vasoconstriction, while the increase in volume is the result of a transient increase in cardiac output and a passive distention of the vascular bed.

The sensitivity of vasomotor responses varies considerably in different persons. Variations in the same individual have been observed from time to time.

The vessels of the upper part of the body are more sensitive to physical, chemical, and nervous stimuli than those of the lower part of the body.

The blood flow induced by local heat of 43° C. is greater in the hand and foot than in the forearm and calf even when the mass of muscle present in the forearm and calf is disregarded and when the blood flow is recorded as cubic centimeters per minute per 100 sq. cm. of surface area.

Local heat of 43° C. produces nearly complete vasodilatation in the skin, but only relatively slight vasodilatation in the underlying muscles.

Exercise is a very effective stimulus for producing vasodilatation in the muscles, but not in the skin. The ability of the muscle vessels to dilate in response to exercise is not appreciably influenced by varying the external temperature between 32° and 43° C.

Pitressin, 1 c.c. intramuscularly, causes as great a decrease in blood flow in the hand and the foot at 43° C. as does epinephrine. At 43° C. it causes a moderate decrease in flow in the forearm and calf.

Neither epinephrine nor pitressin interferes with the dilatation of the muscle vessels in response to exercise or arterial occlusion.

The observation of Grant and Pearson, that unless the circulation to the hand is completely obstructed the plethysmographic method of measuring blood flow to the forearm is not accurate under all conditions, has been confirmed.

AUTHORS.

Hermann, G.: Changes in S-T and T Configuration in the Course of the Day. Arch. f. Kreislaufforsch. 3: 209, 1938.

Diurnal variation in the S-T segment and the T wave occurred in twenty out of forty-seven patients with hypertension, coronary sclerosis, and angina pectoris. These patients were examined, and it was found that these variations repeat themselves on successive days. The author concludes that these daily variations are a sign of a better outlook than their absence.

KATZ.

Freund, Hugo A., and Skokolov, Raymond: Bundle Branch Block. Arch. Int. Med. 63: 318, 1939.

The entire series of electrocardiograms taken at Harper Hospital over a ten-year period were reviewed. Two hundred and ten cases of bundle branch block and intraventricular block were found. In 179 cases (85.2 per cent) the subsequent course was studied; in the remainder of the cases the patient could not be followed. Using Wilson's criteria for the diagnosis of right bundle branch block, we were able to confirm his observation that that condition is more frequent than was previously supposed. The ratio of males to females in our series was 3 to 2. The largest number of cases occurred in patients in the sixth and seventh decades. About three-fourths of the cases occurred in conjunction with arteriosclerotic heart disease. In 15 per cent of the cases there was evidence of frank coronary occlusion.

Patients for whom the diagnosis of bundle branch block is made come to the hospital for a variety of reasons. The diagnosis is practically never made or even suspected until disclosed by electrocardiographic evidence. Consequently, these patients first present themselves with a previous history ranging from good health to complete disability. Frequently evidence of bundle branch block is discovered in the electrocardiogram of a patient who has no other signs of cardiac disease. In such cases signs or symptoms of cardiac disease may never develop. On the other hand, our records reveal repeated electrocardiograms in cases in which bundle branch lesions suddenly developed and death occurred in a short time.

There is no "clinical picture" of bundle branch block. Although bundle branch block may be discovered in conjunction with what is to all appearances a normal or near normal heart, it is most frequently associated with some degree of cardiovascular disease. Statistics in this regard do not show the absolute facts, because the taking of electrocardiograms is not a routine procedure and in many cases the condition is not discovered at its inception.

In general, it may be said that bundle branch block is most frequently found in conjunction with definite heart disease aside from the bundle lesion. Consequently the prognosis in cases of bundle branch block is at best no better than it is in cases of any form of myocardial disease. How much hazard accrues from the bundle branch block is difficult to estimate. In spite of the fact that a majority of the cases occur in aged persons and in patients suffering from cardiac disease, a fair percentage of patients live for a surprising length of time and without great discomfort.

The most important factors to be considered in determining the prognosis are the general condition of the patient and the physical signs of cardiac damage. Patients who are in good condition and show little or no signs of cardiac embarrassment are not as a rule in immediate danger. Those who are suffering from other degenerative

disease and present findings of myocardial disease, such as cardiac enlargement, cardiac arrhythmia, dyspnea, and peripheral edema, suffer seriously from a bundle branch lesion. Gallop rhythm is an ominous prognostic sign. In cases in which bundle branch block is associated with frank coronary thrombosis, the patients are usually destined to early death.

The larger percentage of patients die within the first year after the discovery of the lesion. Those who survive this first year stand an excellent chance of carrying on for a relatively longer time.

These patients with right bundle branch block lived slightly longer than those with a lesion on the left side. Patients with so-called intraventricular block had a poorer life expectancy than those with complete bundle branch block. This study did not include cases in which there was a minor degree of intraventricular block.

The aged patients seemed to withstand the ill effects of bundle branch block as well as did the younger patients.

When bundle branch block was associated with syphilitic heart disease, the prognosis was poor. Patients with bundle branch block secondary to thyroid or congenital heart disease did much better than the average. The rheumatic and arteriosclerotic patients fared about equally well, the prognosis ranking between the two extremes just cited.

Females, in general, lived longer than males with this lesion. Private and charity patients showed no outstanding differences.

AUTHORS.

Kienle, F.: Correlation of Electrocardiographic and Morphological Studies in the Differentiation of Cardiac Damage, Hypertrophy and Axis Deviation. *Arch. f. Kreislauf.* 4: 19, 1939.

This is a report of seven autopsied cases carefully examined histologically. In six cases of left coronary insufficiency, the electrocardiogram showed S-T depressed in Lead I and sometimes in Lead II. In five of these there was histologic evidence of the coronary insufficiency in the form of distinct scars or fresh infarcts in the left, but not the right, ventricle.

KATZ.

Kamberg, J. A. M.: Changes in Heart Muscle in Coronary Insufficiency (An Anatomico-Clinico-Electrocardiographic Study). *Arch. f. Kreislaufforsch.* 3: 340, 1938.

This is a monograph of over seventy pages. The first part is a critical assay of the theoretical aspects of the subject including a discussion of anatomy and dynamics as it pertains to the problem of coronary insufficiency. This is followed by a discussion of pathologic changes and of the etiology of heart failure. The author then summarizes his experiences based on 300 autopsies of healed heart muscle infarcts and coronary disease. This is supplemented by studies of sixty-three ward patients having coronary sclerosis with or without hypertension or valvular defects and syphilitic coronary mouth closure.

KATZ.

Levine, Samuel A.: Angina Pectoris and Its Relation to Coronary Artery Disease. *New England J. Med.* 219: 743, 1938.

"Angina pectoris" is a useful term, but should be confined to designate patients suffering from a peculiar type of distress in the chest or neighboring structures who are liable to sudden, unexpected death. The diagnosis depends almost entirely on the proper interpretation of symptoms. For this reason, direct inquiry is often

necessary in order to avoid overlooking many cases of angina. The characteristic complaints may be so mild or may have occurred so long ago that they are not mentioned by the patient. This accounts for the frequent occurrence of sudden death in patients with cardiac illness in whose cases the diagnosis of angina was overlooked.

Except for a few conditions like paroxysmal rapid heart action, hyperthyroidism, anemia, and aortic valvular disease, angina is always associated with pathologic changes in the coronary arteries. Even in the conditions just mentioned these vessels are often involved.

Angina pectoris is not synonymous with sclerosis of the coronary arteries, for the former is a functional state and the latter is a structural one. The latter may be present in the absence of the former.

Spontaneous attacks of angina may involve factors, especially neurogenic ones, different from those which obtain when attacks are reproduced deliberately by performing functional tests such as the two-step test.

AUTHOR.

Whitehill, M. Richard, Longcope, Warfield T., and Williams, Russell: **The Occurrence and Significance of Myocardial Failure in Acute Hemorrhagic Nephritis.** Bull. Johns Hopkins Hosp. 64: 83, 1939.

From a study of 138 patients, mostly young adults, suffering from the form of acute hemorrhagic nephritis that follows directly upon an active infection due usually to hemolytic streptococci, it has been observed that circulatory insufficiency often forms an integral part of the illness. It is characteristic that evidences of circulatory failure may appear at the onset or during the first few days of the disease. These manifest themselves as dyspnea which may become paroxysmal or progress to orthopnea, by enlargement of the heart, accompanied by alterations in the impulses and sounds, by elevation of venous pressure, and by enlargement of the liver.

The circulatory failure may well lead to an increase of subcutaneous edema, or to cerebral or pulmonary edema, and may produce other deleterious effects such as interference with the function of the injured kidneys. These conditions are uncommon in mild attacks of nephritis, frequent in moderately severe attacks, and present in the majority of cases of severe acute nephritis. The use of digitalis in full doses has seemed to benefit some of these patients with severe circulatory failure.

AUTHORS.

Thomas, Caroline Bedell, and France, Richard: **A Preliminary Report of the Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever.** Bull. Johns Hopkins Hosp. 64: 67, 1939.

Sulfanilamide was given continuously during the course of two winters to thirty individuals with recent history of acute rheumatic fever. The drug was taken daily over a seven months' period in a dosage of 15 to 20 grains without ill effects. None of the patients had a major attack of acute rheumatic fever or an acute beta hemolytic streptococcal infection while taking sulfanilamide. Of thirty control patients, four developed five major attacks of rheumatic fever during the same period, one was hospitalized because of an acute beta hemolytic streptococcal infection, and three others had acute illnesses which might have been of a rheumatic character. It is recognized that the group studied is too small to permit definite conclusions concerning the efficacy of sulfanilamide in preventing attacks of acute rheumatic fever, but the results are encouraging and warrant further studies along this line.

AUTHORS.

Coburn, Alvin F., and Moore, Lucile V.: **The Prophylactic Use of Sulfanilamide in Streptococcal Respiratory Infections, With Especial Reference to Rheumatic Fever.** *J. Clin. Investigation* 18: 147, 1939.

Sulfanilamide appeared to give complete protection to a colony of guinea pigs against spontaneous lymphadenitis with Group C hemolytic streptococcus. Sulfanilamide seemed to protect about two-thirds of the animals which received a large dose of the same organisms intranasally, and modified the disease in the remaining third.

During the course of the study there were no drug symptoms, no frank streptococcal infections, and no attacks of acute rheumatism. Sulfanilamide did not prevent the occurrence of a number of "common colds," one pneumococcus ear infection, and one severe bronchitis of unknown etiology.

These observations showed that quiescent rheumatic subjects can be maintained for many months at a high blood sulfanilamide level without demonstrable ill effects. These patients were visited by their families, were exposed to 2 patients with streptococcal infections who were introduced into The Pellman Home, and lived in close proximity with a carrier of hemolytic streptococcus and with six nonmedicated patients who had positive cultures or rheumatic activity or both at some time during the experiment. Only one of the twenty-six medicated patients contracted an infection with hemolytic streptococcus in the throat flora. Twenty-five highly susceptible rheumatic children were maintained in good health throughout the winter and spring months.

This group of twenty patients appeared to escape streptococcal respiratory infection although a number of them had "common colds" and one developed measles. They also escaped clinical evidence of rheumatic fever. Their freedom from rheumatic activity can best be visualized from the record of their sedimentation rates, given in Table VII.

AUTHOR.

Gauld, Ross L., Ciocco, Antonio, and Read, Frances E. M.: **Further Observations on the Occurrence of Rheumatic Manifestations in the Families of Rheumatic Patients.** *J. Clin. Investigation* 18: 213, 1939.

Facts have been presented relative to the high incidence of rheumatic disease in the families of ninety-six rheumatic children. The percentage of persons with a rheumatic history, who had parents with a similar history, was found to be consistent in two generations of these families and was 3.7 times as high as that found in a group of control families.

The offspring of the grandparents of the rheumatic and control index cases were studied to see if any relationship was present between the type of mating with respect to rheumatic disease and the percentage of children who were rheumatic. When one or both parents had a history of rheumatic manifestations, a greater percentage of the offspring was rheumatic than was found in the offspring of parents who gave no history of rheumatic disease.

The percentage of female offspring of rheumatic mothers who had rheumatic manifestations was found to be almost twice as high as in the male offspring of these mothers.

A greater percentage of persons with rheumatic disease was found among the maternal aunts and uncles than was found among the paternal aunts and uncles of rheumatic index cases.

These findings suggest that hereditary constitution may play a role in the predisposition to this disease. The evidence here presented does not, however, exclude the possibility that infection plays an important role, and that exposure may be the predominating factor.

AUTHORS.

Kissane, Ray W., Koons, Ruth A., and Mahanna, Donald L.: *The Role of Syphilis in Coronary Artery Sclerosis, Occlusion and Angina Pectoris*. *Urol. & Cutan. Rev.* 63: 3, 1939.

A review of 5,859 autopsies, divided into syphilitic and nonsyphilitic groups, revealed the incidence of coronary artery sclerosis in the syphilitic group to be approximately four times greater than that of the nonsyphilitic group. However, this cannot be considered as evidence that syphilis is an important secondary factor in the production of coronary artery disease.

The incidence of coronary artery occlusion in the syphilitic group as compared to the nonsyphilitic group was slightly greater but was considered coincidental because of the small number of syphilitic cases against the much greater number of nonsyphilitic cases.

A study of 3,329 clinical cases, divided into syphilitic and nonsyphilitic groups, revealed the incidence of angina pectoris to be almost ten times greater in the nonsyphilitic group than in the syphilitic group.

It is evident that syphilis is not a primary or secondary factor in the production of coronary artery occlusion or angina pectoris.

AUTHORS.

Stern, Neuton S.: *Arteriosclerosis: Considerations as to Etiology*. *Southern Med. J.* 32: 370, 1939.

There are reasons for believing that vasa vasorum in the walls of arteries extend through the media and the intima as well as the adventitia. The occlusion and inflammation of the vasa vasorum cause the lesions described as arteriosclerosis. The occlusion may be caused by small particles, such as emboli, clumps of bacteria, fibrin particles, fat globules, clumps of white blood cells, phagocytes, pigments, cell detritus, and nuclear fragments. In addition a number of other possible mechanisms of blocking of the lumens of vasa vasorum are discussed, particularly with reference to diabetes mellitus, obesity, hypertension, and old age. In this manner the author attempts to unify the various theories which have been advanced to explain the development of arteriosclerosis.

NAIDE.

Rook, A. F., and Dawson, D. J.: *Hypotension and Flying*. *The Lancet* 2: 1503, 1938.

Hypotension may be said to be present when the systolic blood pressure is below 110 mm. Hg or the diastolic below 70 mm. Hg. Moderate grades of hypotension are considered to be present if the systolic level is between 110 and 100 mm. Hg or the diastolic between 70 and 60 mm. Hg; severe grades when the systolic pressure is below 100 mm. Hg or the diastolic below 60 mm. Hg.

Hypotension is sometimes accompanied by symptoms, such as postural giddiness, and, when so associated, is an absolute bar to all flying. An isolated finding of a severe grade of hypotension is compatible with good health but always calls for considerable caution when assessing for flying duties.

Hypotensive persons may be divided into two ill-defined groups: (a) occasional hypotensives, and (b) persistent hypotensives. (a) Occasional hypotension is not uncommon and is found in a large proportion of young adults when repeated examinations are made. As an isolated finding moderate grades are of little importance so far as flying is concerned. (b) Persistent hypotension is comparatively rare. It is not necessarily, or even usually, permanent but lasts only for a variable period. It may be associated with symptoms of hypotension or with some underlying disease, in which case it is a bar to flying. It is, however, compatible with good health, and then piloting duties may be permitted.

It is probable that the ability of the cardiovascular system to withstand centrifugal effects during flight depends largely on its power to react rapidly to stress. This power is as necessary for the person with normal blood pressure as for the hypotensive.

AUTHORS.

Westcott, F. H., and Wright, I. S.: Tobacco Allergy and Thromboangiitis Obliterans. *J. Allergy* 9: 555, 1938.

The authors found no evidence suggesting that thromboangiitis obliterans was related to tobacco sensitivity. Skin tests and reactions were no more frequent in a group of patients with this condition than in a control group.

McCULLOCH.

Mendlowitz, Milton: Some Observations on Clubbed Fingers. *Clin. Sc.* 3: 387, 1938.

The response of the blood vessels in clubbed fingers to environmental temperature changes is qualitatively normal and the maximum heat eliminations of the hands of patients with clubbed fingers are within normal limits.

The maximum heat elimination and hence the blood flow of the distal phalanges of clubbed fingers secondary to lung or congenital heart disease are usually increased.

The digital arterial pressure is increased and the brachial-digital arterial pressure gradient decreased in clubbing secondary to lung or congenital heart disease. In hereditary clubbing these pressures and gradients are normal.

The blood flow of the unilaterally clubbed finger tip, as indicated by maximum heat elimination may be increased or decreased. No significant change was found in the blood pressure gradient except for a bilateral decrease in a case interpreted to be bilateral clubbing with acceleration of the process in the fingers of one hand due to a sympathetic nerve lesion.

AUTHOR.

Homans, John: Varieties of Thrombophlebitis of the Limbs. Their Origin, Course and Treatment. *Am. J. Surg.* 44: 3, 1939.

This is an excellent account of the known varieties of thrombophlebitis. The factors involved in the development of thrombophlebitis are mentioned. Each type is described and treatment is discussed.

NAIDE.

Weir, David R.: Polyarteritis Nodosa. *Am. J. Path.* 15: 79, 1939.

A case of polyarteritis nodosa is reported with clinical and pathologic findings. A number of unusual features were found in the gross and microscopic examination. These unusual features are: (1) Evidence that the primary lesion occurred in the intima and inner layers of the media and progressed outward through the wall to the adventitia; (2) occurrence of all stages of arteritis from the earliest acute to the healed, but restriction of the lesions in each individual organ to roughly one stage; (3) remarkable parenchymatous lesions of the lungs and spleen; and (4) resemblance of the gross autopsy findings to widespread tuberculosis. In no instance did the disease process involve arteries greater than 1.5 mm. in diameter.

The findings in this case and evidence presented by others make it reasonably certain that the lesions are not primarily periarterial. The author agrees with the suggestion of others that the name polyarteritis nodosa be substituted for the misnomer, periarteritis nodosa.

NAIDE.

Burwell, C. Sidney, Strayhorn, W. David, Flickinger, Don, Corlette, Marvin B., Bowerman, Earl P., and Kennedy, J. Allen: *Circulation During Pregnancy*. Arch. Int. Med. 62: 979, 1938.

Observations on the pulse rate, the systemic blood pressure, the vital capacity, the arteriovenous difference, and the cardiac output made for four women during the course of pregnancy, and in the puerperium, may be summarized as follows:

The basal pulse rate is higher during pregnancy than after delivery; the basal blood pressure (particularly the diastolic phase) is lower during pregnancy than after its termination.

The cardiac output is increased, by as much as 50 per cent or even more, during the period of maximum increase. This increase is usually demonstrable by the third or fourth month. In the last weeks of pregnancy there is a fall in the cardiac output toward normal, and after delivery it is within the limits usual for nonpregnant women.

The increase in output is greater in proportion than the increase in oxygen consumption; therefore the arteriovenous oxygen difference is diminished.

The observations on venous pressures in pregnant women may be summarized as follows:

Venous pressures are nearly the same in the arm and in the leg in supine persons, both normal persons and patients with central obstruction, leading to general elevation of the venous pressure.

Difference between these pressures may exist when there is a condition affecting the venous return from a part of the body, such as a mediastinal or pelvic tumor.

In pregnant women by the beginning of the second trimester the pressure in the leg is notably higher than that in the arm. It continues high throughout pregnancy, but after delivery it is found to be no higher than the pressure in the arm.

These observations on animals may be summarized as follows:

Pressure in the femoral veins is elevated during pregnancy; that in the uterine veins is higher than that in the femoral veins.

These changes are not due to an increase in general intra-abdominal pressure.

The femoral pressure may be lowered if the uterus is elevated and supported; it may be further lowered if the uterus is excised and its vascular connections are severed.

Blood from the veins draining the pregnant uterus tends to exhibit an oxygen content that is high in relation to that of the blood in the right ventricle.

The demonstrated phenomena of the circulation in pregnant women and pregnant animals, plus the available knowledge concerning the structure of the placenta, lead to the conclusion that the changes in the circulation during pregnancy are in the main to be ascribed to two mechanisms: (1) an arteriovenous leak through the placenta and (2) an obstruction to venous return by the enlarged uterus.

AUTHORS.

Mayer, Karol: *An X-ray Inquiry Into the Genesis of the Current of Venous Blood and Lymph*. Radiology 32: 275, 1939.

The arterial pulse in any organ is transmitted to adjacent tissues. With every beat the suddenly growing pressure produces greater rigidity in the region surrounding the venous and lymphatic vessels. Since the direction of least resistance is toward the heart, the increased pressure on the veins and lymphatics, with each beat, causes a movement of blood and lymph in the direction of the heart.

NAIDE.

McGuire, Johnson, Shore, Rose, Hauenstein, Virgil, and Goldman, Fred: Relation of Cardiac Output to Congestive Heart Failure. Arch. Int. Med. 63: 290, 1939.

In nineteen of twenty cases of congestive heart failure the cardiac output was subnormal, the mean value being 1.52 ± 0.06 liters per square meter per minute, while in control cases the mean was 2.16 ± 0.03 liters.

In the groups of patients with congestive failure of varying severity there was a trend toward reduction of cardiac output with the severer manifestations of failure.

AUTHORS.

Heim de Balsac, R.: Anatomical-Radiological Study of the Thoracic Aorta. Presse méd. 45: 1749, 1937.

This is a study of the aorta by contrast media injected post mortem and by casts. The changes determined by age and by the different shapes of the thorax are described in detail.

JENSEN.

Stevenson, C. A.: The Use of Roentgen Therapy in the Carotid Sinus Syndrome. Radiology 32: 209, 1939.

Five patients with carotid sinus syndrome received roentgen therapy, with definite prophylactic value in each.

NAIDE.

Smithwick, Reginald H.: Medical Progress: Surgery of the Sympathetic Nervous System. N. Eng. J. Med. 220: 475, 1939.

This is a review of the applications of surgery of the sympathetic nervous system to peripheral vascular disease, anterior poliomyelitis, hyperhidrosis, Hirschsprung's disease, essential hypertension, pain in the head, face and arms, causalgia, angina pectoris, abdominal visceral pain, and genitourinary tract pain.

NAIDE.

Wald, Maurice H., Lindberg, Howard A., and Barker, M. Herbert: The Toxic Manifestations of the Thiocyanates. J. A. M. A. 112: 1120, 1939.

After ten years' experience with cyanate therapy in hypertension, carefully controlled by determination of the blood content of the drug, the authors present an analysis of the literature on the subject of its toxicity and make suggestions for the clinical guidance to the toxicology and therapeutics of this salt. The beneficial action of thiocyanates in cases of hypertension depends in part on their peculiar toxicology. An attempt is made to differentiate those toxic signs and symptoms which might occur normally in the hypertensive person from those which occur directly as a result of cyanate intoxication.

Symptoms which appear during thiocyanate therapy must be interpreted in the light of the level of the blood cyanates. Without blood cyanate determinations, this drug should not be used.

NAIDE.

Book Review

THE HEART IN PREGNANCY: By Julius Jensen, M.D., Ph.D. (in Medicine), University of Minnesota, M.R.C.S (England), L.R.C.P. (London). Assistant Professor of Clinical Medicine, Washington University School of Medicine; Assistant Physician to Barnes Hospital; Physician to St. Louis Maternity Hospital and St. Louis City Hospital. 371 pages, \$5.50. St. Louis, 1938, The C. V. Mosby Company.

There has been a great need for some such book as this on the subject of heart disease and pregnancy, to bring together the many scattered observations which bear on the physiology of the circulation of the pregnant woman and the effects of pregnancy upon the patient with heart disease. One might wish at times that the references to the literature did not extend back beyond the beginnings of our present concepts of heart disease, though perhaps there may be value in calling attention to the abandonment of former concepts, thus teaching us to be more critical of the ones to which we now hold. Most of the older literature cited has little more than historical interest, and serves at times to obscure the more modern, and, we hope, more firmly grounded observations. The review of the modern literature is very well conducted, and the opinions of the different observers well correlated. The author's critical attitude is conservative and tends to point out the need of further investigations and the lines along which these should be projected. His application of the statistical method to the case reports in the literature leads at times to interesting and important conclusions. Owing to the caution with which he handles the statistics, one is usually ready to agree with these conclusions. At other times the material upon which the different case reports have been based has been collected by authors with such different standards, and in hospitals with such different types of clientele, that they cannot be logically grouped to form a basis for statistical conclusions. The author is aware of this source of error and discounts its results as much as possible, but it always remains an inherent and unaccountable source of weakness in his conclusions.

The causes for the increased cardiac work during pregnancy and what is known of the mechanism whereby the heart meets these demands are discussed. When all is said and done, our knowledge on these subjects is meager. There is a profitable review of the effects of pregnancy upon the normal heart and circulation which will serve as a basis for an understanding of the changes that might be expected in a diseased heart during pregnancy. There is an interesting discussion of the frequency and importance of cardiac arrhythmia during pregnancy.

Over a third of the book is occupied with an excellent discussion of the various aspects of rheumatic heart disease which result from the advent of pregnancy and labor. The section on the diagnosis of rheumatic valvular disease seems to place much less emphasis upon the observation of physical signs than do the Criteria for the Diagnosis of Heart Disease of the New York Heart Association. The condition described as functional heart disease of pregnancy warrants special attention, for it is so rarely described in the modern obstetrical-cardiac literature as to raise a doubt as to its occurrence. The reviewer has not seen such a case. The appearance of dyspnea, tachycardia, and edema during pregnancy in a patient with heart disease cannot "always indicate that a damaged heart is becoming embarrassed," for such symptoms appear in many healthy women during pregnancy, and it is likely that they may arise in a woman with heart disease by the same mechanism as in the woman without this handicap.

There is a good discussion of the management of decompensation during pregnancy and the indications for interrupting pregnancy because of heart disease. The semirecumbent position during delivery is mentioned, but its importance is scarcely sufficiently emphasized, especially for certain patients who show a tendency to dyspnea when lying flat. Forceps and cesarean section and anesthesia receive satisfactory discussions. Cesarean section is recommended as the safest way of relieving an embarrassed heart of the strain of labor. It is interesting to read that there is "no evidence that lactation has done harm where compensation has been adequate," for this viewpoint is sufficiently considered by obstetricians. The effects of pregnancy upon degenerative heart disease, hypertension, congenital heart disease, kyphoscoliosis, and syphilitic heart disease are also discussed.

The bibliography occupies over fourteen pages, and, although a certain amount of this is only of historical interest, it includes all of the worth-while modern contributions of European and American authors. Such a compilation in itself is of great value to the student of the overlapping terrain of obstetrics and cardiology. Anyone who has had experience in this field or who wishes to acquire knowledge of it will find this book a most valuable source of information and reference.

HAROLD E. B. PARDEE.

Books Received

ALLGEMEINE ELEKTROKARDIOGRAPHIE, Ed. 4, by Prof. Dr. Eberhard Koch, Bad-Nauheim, 1939, Theodor Steinkopff, 41 pp., 41 illustrations, RM 2.25.

ÉLECTROCARDIOGRAPHIE EXPERIMENTALE. Application à La Physio-Pathologie du Cœur Dualité du Cœur Arythmies, by Docteur E. Desomer, Paris, 1938, Masson et Cie, 142 pp., 77 illustrations, 60 francs.

American Heart Association, Inc.

RADIO CITY

50 WEST 50TH STREET, NEW YORK, N. Y.

DR. WILLIAM D. STROUD
President

DR. PAUL D. WHITE
Vice-President

DR. HOWARD B. SPRAGUE
Secretary

DR. WALTER W. HAMBURGER
Treasurer

BOARD OF DIRECTORS

DR. T. HOMER COFFEN Portland, Ore.
DR. CLARENCE DE LA CHAPELLE New York City
DR. WILLIAM DOCK San Francisco
DR. HUGH FARRIS St. John, N. B., Canada

DR. WALTER W. HAMBURGER Chicago
DR. GEORGE R. HERRMANN Galveston
*DR. EMMET F. HORINE Louisville
DR. T. DUCKETT JONES Boston
*DR. EMANUEL LIBMAN New York City
DR. DREW LUTEN St. Louis
DR. GILBERT MARQUARDT Chicago
*DR. H. M. MARVIN New Haven

*DR. EDWIN P. MAYNARD, JR. Brooklyn
DR. THOMAS M. McMILLAN Philadelphia
DR. JONATHAN MEAKINS Montreal
*DR. FRANKLIN NUZUM Santa Barbara
DR. STEWART R. ROBERTS Atlanta
*DR. ROY W. SCOTT Cleveland
*DR. HOWARD B. SPRAGUE Boston
*DR. WILLIAM D. STROUD Philadelphia
DR. LOUIS VIKO Salt Lake City
*DR. PAUL D. WHITE Boston
DR. FRANK N. WILSON Ann Arbor
*DR. IRVING S. WRIGHT New York City
DR. WALLACE M. YATER Washington, D. C.

DR. H. M. MARVIN, *Chairman, Executive Committee
and Acting Executive Secretary*

GERTRUDE P. WOOD, *Office Secretary*

TELEPHONE CIRCLE 5-8000

THE American Heart Association, sponsor of the first International Health Broadcast, stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is \$5.00 a year and journal membership at \$10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

**Executive Committee.*

INDEX TO VOLUME 17

A

- Abnormality, congenital (*see* Heart, abnormality)
- Abramson, David I., Zazeela, H., and Marrus, J., 194
- Acetyl-beta-methylcholine, effect of, on frog's heart, 305
chloride, iontophoresis, treatment of deep thrombophlebitis and chronic leg ulcers with, 316
- Acetylcholine, administration of strophanthin and, comparison of changes in human electrocardiogram following and during vagal stimulation, 515
- Acidosis, effect of alkalosis and, upon human electrocardiogram, 169
- Acoustic phenomena of mitral valves, 119*
- Age, relation of, to renal pressor substance, 383*
- Alam, M., and Smirk, F. H., 124*
- Alkalosis, effect of, and acidosis upon human electrocardiogram, 169
- Allen, Edgar V., and Fatherree, T. J., 752*
- , Roth, G. M., and MacLay, E. V., 121*
- American Heart Association announcement, 130
- Andrews, Howard L., 599
- Anesthesia, sodium amytal, digitalis assay in cats under, 632*
- Aneurysm, 125*
of aortic arch, absence of pulse in vessels of upper extremities and neck in, 716
arteriovenous, 640*
clinical aspect of, 512*
of heart, 569
parietal, of heart, 252*
- Angina pectoris, coronary artery disease and, 254*
problem of, in negro, 711
relation to coronary artery disease, 757*
role of syphilis in coronary artery sclerosis, occlusion and, 760*
- Anoxemia, induced, use of, electrocardiographic changes caused by, as test of coronary insufficiency, 634*
- Anoxemia, induced—Cont'd
gradually, electrocardiographic response to, 655
- Anthony, A. J., and Lent, W., 126*
- Aorta, abnormality of, coarctation of (nonclinical type), associated with congenitally bicuspid aortic valve, 444
with stenosis of right subclavian artery, 628
congenital, persistent right dorsal (terminating in the lower lobe of the right lung), fatal hemorrhage from, 496
- arch of, aneurysm of, absence of pulse in vessel of upper extremities and neck in, 716
- arteriosclerosis of, in rabbits, 753*
- coarctation of, nonclinical type of, associated with congenitally bicuspid aortic valve, 444
with stenosis of right subclavian artery, 628
- thoracic, study, anatomical-radiological, 763*
- valve of, calcareous disease of, 138
congenital atresia of, without septal defect, 502
visualization of, by roentgenographic overpenetration, 512*
- Arteriosclerosis, aortic, in rabbits, 753*
blood flow and vasomotor reactions in foot, in health, in, and in thromboangiitis obliterans, 256*
of coronary arteries in relation to age, disease, and constitution, 126*
etiology of, 760*
- Artery, bronchial, pulmonary atresia and hypertrophy of, 384*
coronary, atherosclerosis of, in relation to age, disease, and constitution, 126*
collateral blood flow in, immediate effect of occlusion of coronary veins in, 379*
combined thrombo-emboli of, 124*
disease of, analyzed post mortem, influence of economics and sex, 10
and angina pectoris, 254*
and relation to, 757*
occlusion, acute, of, partial and complete heart block, in, 123*

An asterisk () after a page number indicates the reference is an abstract and not an original article.

Artery, coronary—Cont'd

- role of syphilis in coronary artery sclerosis, and angina pectoris, 760*
 - with and without pain, 253*
 - sclerosis of, 387
 - occlusion, and angina pectoris, role of syphilis in, 760*
 - thrombosis of, in young women, 382*
 - early rise of blood pressure in, 103
 - ventricular fibrillation as cause of sudden death in, 735
 - disease, diffuse, of, with hypertension, 126*
 - distributing, media of, study of structure of, by method of microdissection, 251*
 - lesions, acute, of, in rabbits with experimental renal hypertension, 120*
 - pulmonary, atresia of, and hypertrophy of bronchial arteries, 384*
 - embolism of, transient bundle branch block and other electrocardiographic changes in, 423
 - sclerosis, primary of, 755*
 - subclavian, right, coarctation of aorta, with stenosis of, 628
 - thrombosis of, following simple contusion, 111
- Atherosclerosis (*see* Arteriosclerosis)
- Auricle, right, 385*
- Auricular fibrillation, effect of, on course of hypertension, 256*
- flutter and complete heart block, 114
- Ayman, David, and Goldshine, A. D., 256*

B

- Bähr, E., 126*
- Baker, Thomas W., and Williams, F. A., 382*
- Baldes, E. J., Essex, H. E., Herrick, J. F., and Mann, F. C., 754*
- Barker, M. Herbert, Wald, M. H., and Lindberg, H. A., 763*
- Barker, Nelson W., 124*
- Barker, Paul S., Shrader, E. L., and Ronzoni, E., 169
- Barnard, W. G., and East, T., 384*
- Bazett, H. C., 385*
- Bell, G. H., 509*
- Benner, Miriam C., 437
- Bereonsky, Isaac, and Cassio, P., 1
- Berk, Louis H., 569
- Bernstein, Mitchell, and Simkins, S., 218
- Bishop, Louis Faugères, Jr., and Carden, G. A., Jr., 275
- Blair, H. A., and Wedd, A. M., 536
- Bland, Edward F., Gordon, W. H., and White, P. D., 10
- Blinder, S., 238

- Blood, circulation and volume, effect of heat on, 385*
- flow and vasomotor reactions in foot in health, in arteriosclerosis, and in thromboangiitis obliterans, 256*
- in hand, forearm, foot, and calf in response to physical and chemical stimuli, 755*
- in foot, plethysmographic method for quantitative measurement of, 508*
- collateral, in coronary arteries, immediate effects of occlusion of coronary vein on, 379*
- coronary, blood pressure and pulse rate of dog, influence of exercise on, 754*
- measurement in man by pneumocardiographic method of excess of arterial outflow from chest over venous inflow during heart cycle, 536
- peripheral, in man, plethysmographic studies of, 194
- "guanidine" in arterial hypertension, 511*
- oxygen changes following intermittent venous occlusion, 401
- pressure and pulse rate following bleeding, 632*
- aortic, intramyocardial pressure and its relation to, 632*
- cold as standard stimulus of, 256*
- effect of tobacco on, as measured by standard smoking test, 124*
- high, problem of, in man, 638*
- pulse rate, and coronary blood flow of dog, influence of exercise on, 754*
- raising reflexes in health, essential hypertension and renal hypertension, 214*
- regulation of, aspects of, and experimental arterial hypertension, 641*
- rise of, early, in coronary thrombosis, 103
- stimulus, use of cold as standard, 256*
- venous, antecubital and femoral, effect of mediastinal lesions on, 57
 - direct method for determination of; relationship of tissue pressure to venous pressure, 634*
 - immediate effect of mercurial diuresis on, 187
 - relationship of tissue pressure to, 634*
- in thromboangiitis obliterans, 121*
- venous, and lymph, x-ray inquiry into genesis of current of, 762*
- volume and circulation, effect of heat on, 385*

Blood volume—Cont'd

- I, experimental changes in: blood pressure and pulse rate following bleeding, 632*
 - vessels, congenital abnormality of, bilateral carotid sinus denervation in patient having syncopal attacks and, 69
 - distensibility of, of extremities, 126*
 - intracranial, lesions of, 40
 - pulse absent in, of upper extremities and neck in aneurysm of aortic arch, 716
- Bock, H., 508*
- Body build and heart size, 616
- warming of, observations on vascular responses of human limb to; evidence for sympathetic vasodilator nerves in normal subject, 127*
- de Boer, S., 383*
- Boland, Edward W., and Williams, F. A., 512*
- Book review, 764
- Bowerman, Earl P., Burwell, C. S., Strayhorn, W. D., Flickinger, D., Corlette, M. B., and Kennedy, J. A., 762*
- Boylston, G. A., McEwen, E. G., and Ivy, A. C., 752*
- Breathing, Cheyne-Stokes, concerning, 380*
- Brill, I. C., 254*
- Bronchus, modification of trachea and, in mitral disease, 257*
- Bruenn, Howard G., Levy, R. L., and Russell, N. G., Jr., 634*
- Brüner, H., and Mertens, W., 632*
- Bundle branch block, prognosis of, 275
- Burch, George E., and Sodeman, W. A., 21, 634*
- Burwell, C. Sidney, Strayhorn, W. D., Flickinger, D., Corlette, M. B., Bowerman, E. P., and Kennedy, J. A., 762*
- C
- Calcareous disease of aortic valve, 138
- Calciferol (*see* Vitamin D₂)
- Carden, George A., Jr., and Bishop, L. F., Jr., 275
- Cardiovascular system, disease, hypertensive, diagnosis of, without hypertension, 511*
- involvement, role of treatment of syphilis in prevention of, 286
 - lesions of, in calves fed diet low in magnesium, 120*
- Carleton, H. M., and Maegraith, B. G., 753*
- Carotid sinus, denervation, bilateral, in a patient having syncopal attacks and a congenital vascular anomaly, 69
- syndrome of, use of roentgen therapy in, 763*

- Carr, F. Benjamin, and Levi, H., 243
- Cat method, assay of digitalis by, under sodium amytal anesthesia, 632*
- Chen, K. K., Robbins, E. B., and Worth, H., 507*
- Cheyne-Stokes breathing, 380*
- respiration, pharmacology of, 691
- Childhood, normal chest electrocardiogram in, 635*
- Children, diphtheria affecting Q-T interval in, 508*
- young, enlargement of heart in infants and, 602
- Cigarette, smoking of, 251*
- Cioceo, Antonio, Gauld, R. L., and Read, F. E. M., 759*
- Circulation, adjustment of, clinical studies in, 638*
- coronary, dynamics of, immediate effects of occlusion of coronary veins on, 507*
 - insufficiency of, changes in heart muscle in, 757*
 - test for, use of electrocardiographic changes caused by induced anoxemia as, 634*
 - during pregnancy, 762*
 - effect on, of intravenous injection of fifty per cent dextrose and sucrose solution in patients with heart disease, 542
 - reference to, earliest known, heart and, 259
 - studies on, in pregnancy, 257*
 - study, experimental anatomical-radiological, of, of normal newborn infant by post-mortem shadows, 633*
 - time of, determination of, with lobelin, 121*
 - measurement of, use of magnesium sulfate in, 218
- Clara, M., 126*
- Clark, Charles P., and Ungerleider, H. E., 92
- Clawson, B. J., 387
- Cleland, J. B., 125*
- Coburn, Alvin F., and Moore, L. V., 759*
- , and Pauli, R. H., 255,* 509*
- Coggin, Charles B., Griggs, D. E., and Evans, N., 681
- Cohen, Mandel E., Thomas, K. J., and Hamilton, B. E., 257*
- Colm, A. E., and Macleod, A. G., 305
- Cold as a standard stimulus of blood pressure, 256*
- Collens, William J., and Wilensky, N. D., 624
- Comeau, Wilfred J., Thompson, W. P., and White, P. D., 286
- , Wise, N. B., and White, P. D., 701
- , and White, P. D., 158, 616
- Comroe, B. I., Griffith, J. O., and Zinn, C. J., 633*
- Conduction, time of, correlation between pulse frequency and, as sign of myocarditis, 122*

Conduction—Cont'd
variations in A-V and V-A, dependent upon time relations of auricular and ventricular systole: supernormal phase, 524

Congestion, chronic passive, changes in liver produced by, 512*

Conn, Jerome W., Kline, E. M., and Rosenbaum, F. F., 524

Contusion, of heart, 561
simple, arterial thrombosis following, 111

Conus, pulmonary, stenosis of, with closed fetal passages, 243

Cor biloculare (*see* Heart, abnormality of)

Corlette, Marvin B., Burwell, C. S., Strayhorn, W. D., Flickinger, D., Bowerman, E. P., and Kennedy, J. A., 762*

Coronary occlusion with and without pain, 253*

Cossio, Pedro, 119*

—, and Berconsky, I., 1
Cottenot, P., and Heim de Balsac, R., 633*

Craig, Winchell McK., 641*

Crane, Norman F., Stewart, H. J., Deitrick, J. E., and Thompson, W. P., 128*

—, —, —, and Wheeler, C. H., 127*
Crawford, J. Hamilton, and DiGregorio, N. J., 114

Curb, Dolph L., and Schwab, E. H., 511*
Cyanosis, in mitral stenosis, 1

D

Dack, Simon, Master, A. M., and Jaffe, H. L., 123*

Damin, Gustave J., and Moore, R. A., 508*

Davis, D., 639*
Davison, Richard, Lundy, C. J., and Treiger, I., 85

Dawson, D. J., and Rook, A. F., 760*

Death, sudden, ventricular fibrillation as cause of, in coronary artery thrombosis, 735

Deitrick, John E., Stewart, H. J., Crane, N. F., and Thompson, W. P., 128*

—, —, —, and Wheeler, C. H., 127*
Dewald, Donald, and Gregg, D. E., 379,* 507*

Dextrose, solution, fifty per cent, circulatory effect of intravenous injections of, and sucrose, in patients with heart disease, 542

Diabetes, thromboangiitis obliterans in, 624

Dietrich, H., and Schlomka, G., 121*

Digilio, Victor A., Pescatore, J. A., and Wolffe, J. B., 489

Digitalis, action of, in compensated heart disease, 128*

in uncompensated heart disease, 127*
on precordial lead of electrocardiogram, 252*

assay of, by cat method under sodium amytal anesthesia, 632*
-like glucosides, certain pure, effect of, on frog's heart, 294

DiGregorio, N. J., and Crawford, J. H., 114

Di Palma, Joseph R., and Johnson, J. R., 632*

Diphtheria, influence of, on size of heart and on heart muscle structure, 635*

Q-T interval in, affecting children, 508*

Diuresis, mercurial, immediate effect on venous blood pressure, 187

Donovan, John J., Herndon, R. F., and Vass, A., 553

Dry, Thomas J., and Williams, F. A., 138

DuBois, Delafield, Hoff, E. C., Kramer, T. C., and Patten, B. M., 470

Durant, Thomas M., Ginsburg, I. W., and Roesler, H., 423

E

East, Terrence, and Barnard, W. G., 384*
Eckey, P., and Vorwerk W., 633*

Effusion, serous, multiple, myxedema with, and cardiac involvement, 368

Einthoven triangle, compared with other lead combinations, 634*

Electrocardiogram, changes in, caused by induced anoxemia, use of, as test of coronary insufficiency, 634*

induced by taking of food, 725

S-T and T configuration in course of day, 756*

transient bundle branch block and other, in pulmonary embolism, 423

chest, normal, in childhood, 635*

development of, embryonic heart, 470

Einthoven triangle compared with other lead combinations, 634*

findings by, in cardiac infarctions with various chest leads, 634*

foetal, human, 509*

human, comparison of changes in, following strophanthin and acetylcholine and during vagal stimulation, 515

effect of alkalosis and acidosis upon, 169

in nephritis, acute, 122*

in pericarditis, 122*

lead, precordial, of, action of digitalis on, 252*

Electrocardiogram—Cont'd

- leads, three synchronized, between fixed points on heart projection in chest wall, 508*
 - observation on, in traumatic posterior wall infarct, 755*
 - P-R interval, short, bundle branch block with, from people with organic heart disease, 252*
 - Q-T interval of, in diphtheria affecting children, 508*
 - researches on, 383*
 - response of, to gradually induced oxygen deficiency, 655
 - serial, in contusion of heart, 561
 - studies of, correlation of, and morphology, in differentiation of cardiac damage, hypertrophy and axis deviation, 757*
 - study of, of twins, 701
 - T-wave of, significance of severe anoxic variations of, in healthy subjects, 121*
 - V-wave of, interpretation of, 585
 - variations in A-V and V-A conduction dependent upon time relations of auricular and ventricular systole: the supernormal phase, 524
 - ventricular, complex in, study of, with left axis deviation, 251*
 - extrasystoles induced by electrical stimulation of exposed human heart rotated thirty degrees counterclockwise on the vertical axis, 85
- Electrocardiography, clinical frontiers of, 121*
- Electrode for recording bioelectric potentials, 599
- Elliot, Albert H., Ussher, N. T., and Stone, C. S., 69
- Ellis, Laurence B., and Faulkner, J. M., 542
- Embolism, pulmonary, transient bundle branch block and other electrocardiographic changes in, 423
- Emphysema, arrhythmia, physiologic, of heart in, 121*
- Enghoff, H., and Lindholm, K., 380*
- Epstein, Bernhard S., 512*
- Ergotamine tartrate, use of, complication following, 129*
- Essex, Hiram E., Herrick, J. F., Baldes, E. J., and Mann, F. C., 754*
- Ethridge, Clayton B., Massie, E., and O'Hare, J. P., 383*
- Evans, Newton, Griggs, D. E., and Coggin, C. B., 681
- Exercise, influence of, on blood pressure, pulse rate and coronary blood flow of dog, 754*

Exercise—Cont'd

- role of rest and, in congestive heart failure, 639*
- Exophthalmic goiter, syndrome of, acute rheumatic carditis and heart block, 742
- Extrasystoles (*see* Heart, contraction, ectopic of)

F

- Fatherree, Thomas J., and Allen, E. V., 752*
- , and Hines, E. A., Jr., 1125*
- Faulkner, James M., and Ellis, L. B., 542
- Foetus, human, electrocardiogram of, 509*
- Fineberg, M. H., 494
- Fingers, clubbed, observation on, 761*
- Fitzgibbon, J. P., and Nathanson, M. H., 691
- Flickinger, Don, Burwell, C. S., Strayhorn, W. D., Corlette, M. B., Bowerman, E. P., and Kennedy, J. A., 762*
- Flying, hypotension and, 760*
- Food, taking of, electrocardiographic changes induced by, 725
- France, Richard, and Thomas, C. B., 758*
- Franco, Saverio, and Marzullo, F. R., 368
- Freed, C. C., Suzman, M. M., and Prag, J. J., 384*
- Freund, Hugo A., and Sokolov, R., 756*
- Friedberg, Charles K., and Solval, A. R., 452
- Friedman, M., Katz, L. N., Rodbard, S., and Weinstein, W., 334
- Fry, William E., and Swanson, E. E., 632*
- Foramen ovale, premature closure of, 437

G

- Gardberg, Manuel, and Olsen, J., 725
- Garvin, Curtis F., and Scott, R. W., 375, 431
- Gauld, Ross L., Ciocco, A., and Read, F. E. M., 759*
- Ginsburg, I. W., Durant, T. M., and Roesler, H., 423
- Giustra, Frank X., and Tosti, V. G., 249
- Glucosides, cardiac molecule of, significance of sugar component in, 507*
- digitalis-like, certain pure, effect of, on frog's heart, 294
- Goldblatt, Harry, 512*
- Goldbloom, A. Allen, and Lieberman, A., 638*
- Goldman, Fred, McGuire, J., Shore, R., and Hauenstein, V., 763*
- Goldshine, Archie D., and Ayman, D., 256*
- Goldstein, Raymond J., Hirschhorn, L., and Lisa, J. R., 76
- Goodpastor, William E., 496

- Goormaghtigh, Norbert, and Handovsky, H., 637*
- Gordon, William H., Bland, E. F., and White, P. D., 10
- Gorham, L. W., and Martin, S. J., 252,* 253*
- Grandgérard, R., and Heim de Balsac, R., 512*
- Grant, R. T., and Holling, H. E., 127*
- Gregg, Donald E., and Dewald, D., 379,* 507*
- Griffith, J. O., Zinn, C. J., and Comroe, B. I., 633*
- Griggs, Donald E., Coggin, C. B., and Evans, N., 681
- Gross, Louis: In Memoriam, 749
- Grosse, F., 634*
- Grossman, Edward B., and Williams, J. R., Jr., 383*
- Guanidine, blood content of, in arterial hypertension, 511*
- Guckes, E., and Hollmann, W., 753*

H

- Hadfield, G., 636*
- Hadorn, W., 124*
- Hallman, E. T., Moore, L. A., and Sholl, L. B., 120*
- Hallock, Phillip, and Hebbel, R., 444
- Hamburger, Walter W., 259
- Hamilton, Burton E., Thomas, K. J., and Cohen, M. E., 257*
- Handovsky, Hans, and Goormaghtigh, N., 637*
- Harrison, Tinsley R., Williams, J. R., and Wegria, R., 510*
- Hartog, H. A., 252*
- Hauenstein, Virgil, McGuire, J., Shore, R., and Goldman, F., 763*
- Heart, abnormality, congenital, bicuspid valve, coarctation of aorta, nonclinical type, associated with, 444
- true cor biloculare in identical twins, 249
- clinical observation on, of type called "communication intrauricular," 254*
- premature closure of foramen ovale, 437
- tetralogy of Fallot, 489, 553
- aneurysm of, 569
- parietal of, 252*
- arrhythmia, physiologic, of, in emphysema, 121*
- block, bundle branch, 756*
- prognosis in, 275
- transient and other electrocardiographic changes in pulmonary embolism, 423
- with short P-Q interval in electrocardiogram from people with organic heart disease, 252*
- complete, auricular flutter and, 114
- partial and complete, in acute coronary artery occlusion, 123*

Heart block—Cont'd

- syndrome of exophthalmic goiter, acute rheumatic carditis and, 742
- conduction time of, intraventricular defect of, 379*
- contraction of, measurement in man by pneumocardiographic method of excess of arterial outflow from chest over venous inflow during, 536
- ectopic, of, evaluation of relative duration of systole, 122*
- ventricular, of, induced by electrical stimulation of exposed human heart rotated thirty degrees counterclockwise on its vertical axis, 85
- contusion of, serial electrocardiogram, 561
- damage of, correlation of electrocardiographic and morphological studies in differentiation of hypertrophy and axis deviation, 757*
- disease of, circulatory effects of intravenous injection of fifty per cent dextrose and sucrose solutions in patients with, 542
- compensated, action of digitalis in, 128*
- congenital, clinical diagnosis of, 508*
- organic, bundle branch block with short P-R interval in electrocardiogram from people with, 252*
- rheumatic, incidence of among college students in United States, 381*
- acute, syndrome of exophthalmic goiter and heart block, 742
- chronic, significance of rheumatic activity in, 669
- uncompensated action of digitalis in, 127*
- embryonic, development of electrocardiogram of, 470
- enlargement of, in infants and young children, 602
- reversible of, in a case of congenital cavernous hemangioma, 131
- failure, congestive of, relation of cardiac output to, 763*
- right ventricular hypertrophy, and, in chronic pulmonary disease, 681
- role of rest and exercise in, 639*
- mercurial diuretics in, 494
- frog's, effect of acetyl-beta-methylcholine on, 305
- certain pure digitalis-like glucosides on, 294

Heart—Cont'd

- human, exposed, rotated thirty degrees counterclockwise on its vertical axis, ventricular extrasystoles induced by electrical stimulation of, 85
- hypertrophy of, correlation of electrocardiographic and morphological studies in differentiation of cardiac damage, and axis deviation, 757*
- idiopathic, of, in infancy and in normal growth, cardiac muscle in, 508*
- infarcts of, localization of, in man, 380*
- murmur, systolic, of, follow-up study of, 416
- muscle of (*see* Myocardium)
 - papillary, of, spontaneous rupture of, 106
- myxedema of, multiple serous effusions and, 368
- output of, relation of, to congestive heart failure, 763*
- pain from, 252*
- in pregnancy, 764 (B. rev.)
- pressure, intramyocardial, of, and its relation to aortic blood pressure, 632*
- projection of, in chest wall, three synchronized leads between fixed points on, 508*
- in pulmonary tuberculosis, electrocardiographic consideration, 255*
- reference (earliest known) to, and circulation, 259
- septum of, rupture of, myocardial infarction with, 375
- silhouette of, study of transverse diameter of, with prediction table based on teleoroentgenogram, 92
- size of, and body build, 616
 - evaluation of heart volume determinations by Rohrer-Kahlstorf formula as clinical method of measuring, 158
 - influence of diphtheria on, and on heart muscle structure, 635*
- thyrotropic hormone, experimental influence of, on, 753*
- tumors of, and pericardium, 431
 - primary, of, 728
- valve of, areas of, movement of roentgen-opaque deposits in, 639*
- volume of, determination of, evaluation of, by Rohrer-Kahlstorf formula as a clinical method of measuring heart size, 158
 - minute, of, effect of strophanthin on gaseous metabolism and, in presence of, and in absence of buffer receptors, 633*

Heart volume—Cont'd

- normal, in man, 406
- wall, posterior, of, traumatic infarction of, clinical and electrocardiographic observation on, 755*
- Heat, effect of, on blood volume and circulation, 385*
 - vasodilatation, indirect, induced by, observation concerning mechanism of, 752*
- Hebbel, Robert, and Hallock, P., 444
- Hedley, O. F., 381*
- Heim de Balsac, R., 252,* 385,* 763*
- , and Cottenot, P., 633*
- , and Grandgérard, R., 512*
- , and Routier, D., 254,* 257*
- Helmer, O. M., Kohlstaedt, K. G., and Page, I. H., 15
- Hemangioma, congenital cavernous, reversible cardiac enlargement in a case of, 131
- Hemodynamics, mechanics of, flowing streams with comments on, 753*
- Heninger, B. R., and Matas, R., 131
- Hermann, G., 756*
- Herndon, Richard F., Vass, A., and Donovan, J. J., 553
- Herrick, J. F., Essex, H. E., Baldes, E. J., and Mann, F. C., 754*
- Heumans, C., 641*
- Heymans, Corneille, 120*
- Hines, Edgar A., Jr., and Fatherree, T. J., 125*
- , and Roth, G. M., 124*
- Hirschhorn, Louis, Lisa, J. R., and Goldstein, R. J., 76
- Hoff, Ebbe C., Kramer, T. C., DuBois, D., and Patten, B. M., 470
- Hoff, H. E., and Nahum, L. H., 585
- Holling, H. E., and Grant, R. T., 127*
- Hollmann, H. E., and Hollmann, W., 634*
- Hollmann, W., and Guckes, E., 753*
- , and Hollmann, H. E., 634*
- Holms, Joseph H., and Love, W. S., Jr., 628
- Homans, John, 761*
- Horton, Bayard T., 638*
- , and Mills, J. H., 512*
- Hübener, G., 379*
- Hussey, Hugh Hudson, 57
- Hydronephrosis, rats with, hypertension of, relation of renal pressor substance, 510*
- Hypertension, arterial, blood "guanidine" in, 511*
 - disease, diffuse, with, 126*
 - experimental, 120*
 - aspect of blood pressure regulation and, 641*
 - course of, effect of auricular fibrillation on, 256*
 - diagnosis of hypertensive cardiovascular disease without, 511*
 - essential, mortality rate of, does it increase in, 637*

Hypertension, essential—Cont'd

- selection of cases and results obtained by subdiaphragmatic extensive sympathectomy, 641*
 - experimental, of renal origin in rabbit, 753*
 - genuine, concerning the stimulating material of, 509*
 - of hydronephrotic rats, relation of renal pressor substance to, 510*
 - primary, of lesser circuit, existence of, 755*
 - renal, experimental acute arterial lesions in rabbits with, 120*
 - genesis of, observations on, 334
 - treatment, surgical, of, experimental observations on, 512*
 - vascular, thiocyanate therapy in, 383*
- Hypotension, and flying, 760

I

- Infancy, heart hypertrophy idiopathic in, and in normal growth, cardiac muscle in, 508*
- Infants, enlargement of heart in, and young children, 602
 - newborn, normal, experimental anatomical-radiological study of circulatory system of, by post-mortem shadows, 633*
- Injection, intravenous, circulatory effects of, of fifty per cent dextrose and sucrose solutions in patients with heart disease, 542
- Iontophoresis, acetyl-beta-methylcholine chloride, treatment of deep thrombophlebitis and chronic leg ulcers with, 316
- Ivy, A. C., Boylston, G. A., and McEwen, E. G., 752*

J

- Jaffe, Harry L., Master, A. M., and Dack, S., 123*
- Jensen, Julius, 764
- Johnson, J. Raymond, and DiPalma, J. R., 632*

K

- Kamberg, J. A. M., 757*
- Katz, L. N., Friedman, M., Rodbard, S., and Weinstein, W., 334
- Keeley, J. Kenneth, and Linton, R. R., 27
- Keil, Harry, 635*
- Keith, Norman M., Roseberg, E. F., and Wagener, H. P., 126*
- Kennedy, J. Allen, Burwell, C. S., Strayhorn, W. D., Flickinger, D., Corlette, M. B., and Bowerman, E. P., 762*
- Kidney, blood supply of, anatomy and biology of, 126*

- Kienle, F., 755,* 757*
- Kissane, Ray W., Koons, R. A., and Mahanna, D. L., 760*
- Klein, Charles, Saland, G., and Zurrow, H., 581
- Kline, Edward M., Conn, J. W., and Rosenbaum, F. F., 524
- Kohlstaedt, K. G., Helmer, D. M., and Page, I. H., 15
- von KönigsLöw, E., and Schlomka, G., 122*
- Koons, Ruth A., Kissane, R. W., and Mahanna, D. L., 760*
- Korth, C., 121*
- Kramer, T. C., Hoff, E. C., DuBois, D., and Patten, B. M., 470
- Kugel, M. A., 602
- Kunkel, Paul, and Stead, E. A., Jr., 256,* 508*
- , —, and Weiss, S., 755*

L

- Langendorf, R., and Pick, A., 122,* 511*
- , and Winternitz, M., 122*
- Leads, chest, diagnosis of, myocardial infarct with, and of, 511*
 - various, electrocardiographic findings in cardiac infarctions with, 634*
- Einthoven triangle compared with other combinations, 634*
- precordial, action of digitalis on, 252*
- three synchronised, between fixed points on heart projection in chest wall, 508*
- Le Fevre, Fay A., 111
- Legs, chronic ulcers of, treatment of deep thrombophlebitis and, with acetyl-beta-methylcholine chloride iontophoresis, 316
- Lent, W., and Anthony, A. J., 126*
- Lepeschkin, E., 635*
- Leverton, W. R., 255*
- Levi, Hans, and Carr, F. B., 243
- Levine, Samuel A., 757*
- Levitt, Robert O., and Volini, I. F., 187
- Levy, Robert L., Bruenn, H. G., and Russell, W. G., Jr., 634*
- Lewis, Sir Thomas, 125*
- Lieberson, Abraham, and Goldbloom, A. A., 638*
- Liedholm, K., and Enghoft, H., 380*
- Liljestrand, G., Lysholm, E., Nylin, G., Zachrisson, G. G., 406
- Lindburg, Howard A., Wald, M. H., and Barker, M. H., 763*
- Linton, Robert R., and Kelley, J. K., 27
- Lippincott, Stuart, 502
- Lisa, James R., Hirschhorn, L., and Goldstein, R. J., 76
- Littauer, David, and Wright, I. S., 325
- Liver, changes in, produced by chronic passive congestion, 512*
- Lobeline, determination of circulation time with, 121*

- Longcope, Warfield T., Whitehill, M. R., and Williams, R., 758*
- Love, William S., Jr., and Holms, J. H., 628
- Lundy, Clayton J., Treiger, I., and Davison, R., 85
- Lungs, primary arterial tree of, and cortical destination of its ramification, 512*
- rheumatic, 636*
- Lymph, current of venous blood and, x-ray inquiry into genesis of, 762*
- Lysholm, E. Liljestr nd, G., Nylin, G., and Zachrisson, G. G., 406
- M
- MacLay, Elizabeth V., Roth, G. M., and Allen, E. V., 121*
- Macleod, A. Garrard, 294
- , and Cohn, A. E., 305
- Maegraith, B. G., and Carleton, H. M., 753*
- Magnesium, calves fed diets low in, cardiovascular and other lesions in, 120*
- sulfate, use of, in measurement of circulation time, 218
- Mahanna, Donald L., Kissane, R. W., and Koons, R. A., 760*
- Maher, Chauncey C., Sanders, A., Plice, S. G., and Wosika, P. H., 742
- Mann, Frank C., Essex, H. E., Herrick, J. F., and Baldes, E. J., 754*
- Manometer, with photoelectric registration, 633*
- Margolies, Alexander, and Wolferth, C. C., 639*
- Marrus, Joseph, Abramson, D. I., and Zazeela, H., 194
- Martin, S. J., and Gorham, L. W., 252,* 253*
- Martin, W. C., Tuohy, E. L., and Will, C., 728
- Marzullo, Eugene R., and Franco, S., 368
- Massie, Edward, Ethridge, C. B., and O'Hare, J. P., 383*
- Masshoff, W., 635*
- Master, Arthur M., Dack, S., and Jaffe, H. L., 123*
- Matas, Rudolph, and Heninger, B. R., 1131
- Maurer, Elmer, 716
- May, S. H., 655
- Mayar, Ralph H., 511*
- Mayer, Karol, 762*
- McCarthy, Patrick A., and Saleeby, E. R., 125*
- McCord, William Mellen, and Veal, J. R., 401
- McEwen, E. G., Boylston, G. A., and Ivy, A. C., 752*
- McGuire, Johnson, and Reid, M. R., 640*
- , Shore, R., Hauenstein, V., and Goldman, F., 763*
- McKeown, Hilton J., and Smith, L. B., 561
- Mediastinum, lesions of, effect of, on pressures in antecubital and femoral veins, 57
- Mendlowitz, M., 761*
- Mertens, W., and Br uner, A., 632*
- Metabolism, gaseous, effect of strophanthin on, and heart minute volume in presence and absence of buffer receptors, 633*
- Meyer, F., 633*
- Meyers, Maurice P., and Sokolov, R. A., 316
- Microdissection, method of, study of structure of media of distributing arteries by, 251*
- Mills, John H., and Horton, B. T., 512*
- Moia, B., 251*
- Moore, L. A., Hallman, E. T., and Sholl, L. B., 120*
- Moore, Lucile V., and Coburn, A. F., 759*
- Moore, Robert A., and Damin, G. J., 508*
- Moragues, V., 106
- M ller, A., 753*
- Myocarditis, sign of, correlation between pulse frequency and conduction time as, 122*
- Myocardium, changes in, in coronary insufficiency, 757*
- failure of, occurrence and significance of, in acute hemorrhagic nephritis, 758*
- in idiopathic hypertrophy of heart in infancy and in normal growth, 508*
- infarction of, clinical and electrocardiographic observation on, 253*
- diagnosis of, with aid of chest wall lead, 511*
- electrocardiographic findings in, with various chest leads, 634*
- with rupture of septum, 375
- structure of, influence of diphtheria on size of heart and on, 635*
- Myxedema, with multiple serous effusion and cardiac involvement, 368
- N
- Nahum, L. H., and Hoff, H. E., 585
- Nathanson, M. H., and Fitzgibbon, J. P., 691
- Negro, angina pectoris in, problem of, 711
- Nephritis, acute, electrocardiogram in, 122*
- hemorrhagic, occurrence and significance of myocardial failure in, 758*

- Nerve, peripheral, lesion of, in thromboangiitis obliterans, 124*
- sympathetic vasodilator, fibers of, in upper and lower extremities; observations concerning mechanism of indirect vasodilatation induced by heat, 752*
- in normal subject, evidence for: observations on vascular responses of human limb to body warming, 127*
- vagus, stimulation of, comparison of changes in human electrocardiogram following strophanthin and acetylcholine and, 515
- Nicotine, isolation of, from human urine, 15
- Nielsen, Niels A., and Trier, M., 515
- Nylin, G., Liljestränd, G., Lysholm, E., and Zachrisson, C. E., 406
- Nylin, S., and Sällström, T., 508*
- Nodules, subcutaneous rheumatic, and simulating lesions, 635*
- O
- O'Farrell, P. T., 508*
- O'Hare, James P., Massie, E., and Ethridge, C. B., 383*
- Olsen, Jenny, and Gardberg, M., 725
- Ortiz, Teófilo, 643
- Oxygen, changes in, of blood following intermittent venous occlusion, 401
- deficiency of (*see* Anoxemia)
- P
- Page, Irvine H., Helmer, O. M., and Kohlstaedt, K. G., 15
- Pain, cardiac, 252*
- coronary occlusion, with and without, 253*
- Papaverine hydrochloride, vasodilatory agent in treatment of peripheral vascular disease, 325
- Papyrus, Edwin Smith Surgical, 259
- Patten, Bradley M., Hoff, E. C., Kramer, T. C., and DuBois, D., 470
- Pauli, Ruth H., and Coburn, A. F., 255,* 509*
- Periarteritis nodosa, 125*
- Pericarditis, electrocardiogram in, 122*
- Pericardium, tumors of heart and, 431
- Pescatore, Joseph A., Wolffe, J. B., and Digilio, V. A., 489
- Pick, A., and Langendorf, R., 122,* 511*
- Pickering, G. W., 638*
- , and Prinzmetal, M., 753*
- , and Wilson, C., 120*
- Plethysmogram, method for quantitative measurement of blood flow in foot, 508*
- Plethysmograph, studies by, of peripheral blood flow in man, 194
- Pllice, Samuel G., Maher, C. C., Sanders, A., and Wosika, P. H., 742
- Pneumocardiogram, measurement in man of excess of arterial outflow from chest over venous inflow during heart cycle, 536
- Polyarteritis, nodosa, 761*
- Posture, changes in, changes in skin temperature of extremities produced by, 385*
- Potentials, bioelectric, new electrode for recording, 599
- Prag, J. J., Suzman, M. M., and Freid, C. C., 384*
- Preipitinogen, in serum prior to onset of acute rheumatism, 255*
- Pregnancy, circulation during, 762*
- heart in, 764
- studies on circulation in, 257*
- Pressor substance, is not present in perfusate of ischemic kidneys, 752*
- renal, relation of age to 383,* 752*
- to hypertension of hydronephrotic rats, 510*
- Prinzmetal, Myron, and Pickering, G. W., 753*
- Puddu, Vittorio, 253*
- , and Russafica, A., 252*
- Pulmonary system, chronic disease of, right ventricular hypertrophy and congestive failure in, 681
- Pulse, absence of, in vessels of upper extremities and neck in aneurysm of aortic arch, 716
- frequency, correlation between, and conduction time as a sign of myocarditis, 122*
- rate of, and blood pressure following bleeding, 632*
- influence of exercise on, blood pressure, and coronary blood flow of dog, 754*
- R
- Rodbard, S., Katz, L. N., Friedman, M., and Weinstein, W., 334
- Raynaud's disease and preganglionic sympathectomy, 125*
- Read, Frances E. M., Gauld, R. L., and Ciocco, A., 759*
- Recovery, "supernormal phase" of, in man, 357
- Reid, Mont R., and McGuire, J., 640*
- Renin (*see* Pressor substance, renal)
- Respiration, Cheyne-Stokes, pharmacology of, 691
- Respiratory system, streptococcal infection of, prophylactic use of sulfanilamide in, with especial reference to rheumatic fever, 759*
- Rest, role of, and exercise, in congestive heart failure, 639*

- Rheumatic fever, activity of, significance of in chronic rheumatic heart disease, 669
acute, precipitinogen in serum prior to onset of, 255*
lung in, 636*
manifestation of, further observations on occurrence of, in families of rheumatic patients, 759*
nodules subcutaneous of, and simulating lesions, 635*
report, preliminary, of prophylactic use of sulfanilamide in patients susceptible to, 758*
significance of, prolonged streptococcal antibody development in, 509*
use, prophylactic, of sulfanilamide in streptococcal respiratory infections with especial reference to, 759*
- Rheumatism (*see* Rheumatic fever)
- Robb, Jane Sands, and Robb, R. C., 380*
Robb, Robert C., and Robb, J. S., 380*
Robbins, E. Brown, Chen, K. K., and Worth, H., 507*
- Roentgen ray, therapy by, use of, in carotid sinus syndrome, 763*
- Roentgenogram, inquiry by, into genesis of current of venous blood and lymph, 762*
method of overpenetration, visualization of aorta by, 512*
movement of opaque deposits in heart valve areas, 639*
postmortem, experimental anatomical-radiological study of circulatory system of normal newborn infant by, 633*
- Roesler, Hugo, Durant, T. M., and Ginsburg, I. W., 423
- Rohrer-Kahlstorf formula, evaluation of heart volume determinations by, as a clinical method of measuring heart size, 158
- Ronzoni, Ethel, Barker, P. S., and Shrader, E. L., 169
- Rook, A. F., and Dawson, D. J., 760*
- Rosenbaum, Francis F., Kline, E. M., and Conn, J. W., 524
- Rosenberg, Edward F., Keith, N. M., and Wagener, H. P., 126*
- Roth, Grace M., and Hines, E. A., Jr., 124*
—, MacLay, E. V., and Allen, E. V., 121*
—, Williams, M. M. D., and Sheard, C., 385*
- Rothstadt, L. E., 256*
- Routier, D., and Heim de Balsac, R., 254,* 257*
- Rühl, A., 121*
- Russafiea, Adriana, and Puddu, V., 252*
- Russell, Nelson G., Jr., Levy, R. L., and Bruenn, H. G., 634*
- S
- Saland, Gamliel, Klein, C., and Zurrow, H., 581
- Saleeby, Eli R., and McCarthy, P. A., 125*
- Sällström, T., and Nylin, S., 508*
- Sanders, Alexander, Maher, C. C., Plice, S. G., and Wosika, P. H., 742
- Scherf, D., and Schott, A., 357
- Schlomka, G., and Dietrich, H., 121*
—, and von Königslöw, E., 122*
- Schott, A., and Scherf, D., 357
- Schwab, Edward H., and Curb, D. L., 511*
- Scleroderma, skin changes in, tissue pressure, an objective method of following, 21
- Scott, Roy W., and Garvin, C. F., 375, 431
- Segal, Harry L., 257*
- Septum (*see* Heart, septum of)
- Serous membrane, normal, sounds produced by friction of, 643
- Shapiro, M. J., 416
- Sheard, Charles, Roth, G. M., and Williams, M. M. D., 385*
- Sholl, L. B., Moore, L. A., and Hallman, E. T., 120*
- Shore, Rose, McGuire, J., Hauenstein, V., and Goldman, F., 763*
- Shrader, E. Lee, Barker, P. S., and Ronzoni, E., 169
- Sievert, C., and Westphal, K., 509*
- Simkins, Samuel, and Bernstein, M., 218
- Skin, changes in, in scleroderma, tissue pressure: an objective method of following, 21
temperature, changes in, of extremities produced by changes in posture, 385*
- Smith, F. H., and Alam, M., 124*
- Smith, F. Janney, 735
- Smith, Leslie B., and McKeown, H. J., 561
- Smithwick, Reginald H., 763*
- Smoking, cigarette, 251*
test, standard, effect of tobacco on blood pressure as measured by, 124*
- Sodeman, William A., and Burch, G. E., 21, 634*
- Sodium amytal, anesthesia from, digitalis assay by cat method, 632*
- Solval, Arthur R., and Friedberg, C. K., 452*
- Sokolov, Raymond A., and Freund, H. A., 756*
- , and Myers, M. P., 316
- Sounds, produced by friction of normal serosae, 643
- Staemmler, M., 755*
- Stanojevie, L., 121*
- Stead, Eugene A., Jr., and Kunkel, P., 256,* 508*
- , —, and Weiss, S., 755*

- Steinert, R., 637*
- Stern, Neuton S., 760*
- Stevenson, C. A., 763*
- Stewart, Harold J., Crane, N. F., Deitrick, J. E., and Thompson, W. P., 228*
- , —, —, and Wheeler, C. H., 127*
- Stone, Caleb S., Elliot, A. H., and Ussher, N. T., 69
- Strayhorn, W. David, Burwell, C. S., Flickinger, D., Corlette, M. B., Bowerman, E. P., and Kennedy, J. A., 762*
- Streptococcus, prolonged development of antibody to, in rheumatic fever, 509*
- Strong, Kenneth C., 251*
- Strophanthin, administration of, and acetylcholine, comparison of change in human electrocardiogram following and during renal stimulation, 515
- effect of, on gaseous metabolism and heart minute volume in presence and in absence of buffer receptors, 633*
- Students, college, incidence of rheumatic heart disease among, in United States, 381*
- Sucrose solution, fifty per cent, circulatory effect of intravenous injection of dextrose and, in patients with heart disease, 542
- Sugar, component, significance of, in molecule of cardiac glucosides, 507*
- Sulfanilamide, prophylactic use of, preliminary report of, in patients susceptible to rheumatic fever, 758*
- in streptococcal respiratory infections with especial reference to rheumatic fever, 759*
- Supernormal phase of recovery in man, 357
- variation in A-V and V-A conduction dependent upon time relations of auricular and ventricular systole, 524
- Suzman, M. M., Freud, C. C., and Prag, J. J., 384*
- Swanson, Edward E., and Fry, W. E., 632*
- Sympathetic nervous system, surgery of, medical progress in, 763*
- Sympathectomy, effect of, on vasa vasorum of rat, 633*
- preganglionic, Raynaud's disease and, 125*
- subdiaphragmatic, extensive, result obtained by, in cases of essential hypertension, 641*
- Syncope, attacks of, bilateral carotid sinus denervation in a patient having, and a congenital vascular anomaly, 69
- Syphilis, role of, in coronary artery sclerosis, occlusion, and angina pectoris, 760*
- treatment of, role of, in prevention of cardiovascular involvement, 286
- Systole, evaluation of relative duration, IV. extrasystoles, 122*
- T
- Teleoroentgenogram, study of, transverse diameter of heart silhouette with prediction table based on, 92
- Tetralogy of Fallot, correlation of clinical, roentgenologic and post-mortem findings, 489
- terminal sepsis with crossed emboli in, 553
- Thiocyanates, manifestations, toxic, of, 763*
- therapy by, in vascular hypertension, 383*
- Thomas, Caroline Bedell, and France, R., 758*
- Thomas, K. Jefferson, Cohen, M. E., and Hamilton, B. E., 257*
- Thompson, William Paul, Comeau, W. J., and White, P. D., 286
- , Stewart, H. J., Crane, N. F., and Deitrick, J. E., 128*
- Thromboangiitis obliterans, blood in, 121*
- flow and vasomotor reactions in foot, in health, in arteriosclerosis, and in, 256*
- complications, fatal, in, 125*
- in a diabetic, 624
- lesions of peripheral nerves in, 124*
- outlook in, 638*
- studies on experimental peripheral vascular disease with special reference to, 384*
- tobacco allergy and, 761*
- Thrombophlebitis, deep, treatment of, and chronic leg ulcers with acetyl - beta - methylcholine, chloride iontophoresis, 316
- migrans, 76
- variety of, of limbs, origin, course, and treatment, 761*
- Thyroid, hormone of, experimental influences of, on heart, 753*
- Tissue pressure, objective method of following skin changes in scleroderma, 21
- relationship of venous pressure to, 634*
- Tobacco, allergy to, and thromboangiitis obliterans, 761*
- effect of, on blood pressure as measured by a standard smoking test, 124*

- Tosti, Vincent G., and Giustra, F. X., 249
 Trachea, modifications of, and bronchi in mitral disease, 257
 Treiger, Irving, Lundy, C. J., and Davison, R., 85
 Trier, Mogens, and Nielson, N. A., 515
 Triogram, clinical significance of, 753*
 Tuberculosis, pulmonary, heart in; electrocardiographic consideration, 255*
 Tumor, glomus, 238
 of heart and pericardium, 431
 primary, of heart, 728
 Tuohy, E. L., Martin, W. C., and Will, C., 728
 Twins, electrocardiographic study of, 701
 identical, study of body build and heart size in, 616
 true cor biloculare in, 249

U

- Ulcer, varicose, postphlebotic, surgical treatment, 27
 Ungerleider, Harry E., and Clark, C. P., 92
 Urine, human, isolation of nicotine from, 15
 Ussher, Neville T., Elliot, A. H., and Stone, C. S., 69

V

- Valve, aortic, congenitally bicuspid, coarctation of aorta, nonclinical type, associated with, 444
 calcareous disease of, 138
 stenosis, nonrheumatic calcific of, 452
 mitral, acoustic phenomena of, 119*
 disease of, modification of trachea and bronchi in, 257*
 stenosis of, cyanosis in, 1
 Vasa vasorum, effect of sympathectomy on, of rat, 623*
 Vascular system, peripheral disease, experimental, of, studies on, with special reference to thromboangiitis obliterans, 384*
 papaverine hydrochloride as vasodilatory agent in treatment of, 325
 thermal reflex vasodilatation test in, 581
 reactions of blood flow and, in foot, in health, in arteriosclerosis, and in thromboangiitis obliterans, 256*
 response of, of human limb, to body warming; evidence for sympathetic vasodilator nerves in normal subject, 127*
 Vasodilatation test, thermal reflex in peripheral vascular disease, 581

- Vasomotor system, reactions of, and blood flow, in foot, in health, in arteriosclerosis, and in thromboangiitis obliterans, 256*
 in hand, forearm, foot and calf, in response to physical and chemical stimuli, 755*
 Vass, Aloysius, Hernden, R. F., and Donovan, J. J., 553
 Veal, J. Ross, and McCord, W. M., 401
 Veins, coronary, occlusion of, immediate effects of, on collateral blood flow in coronary arteries, 379*
 on dynamics of coronary circulation, 507*
 occlusion, intermittent, of, blood oxygen changes following, 401
 Ventricle, fibrillation of, as cause of sudden death in coronary artery thrombosis, 735
 right, hypertrophy of, and congestive failure in chronic pulmonary disease, 681
 Vitamin D₂, effect of, on a dog, 637*
 Volini, Italo F., and Levitt, R. O., 187
 Von Storch, Theodore J. C., 129*
 Vorwerk, W., and Eekey, P., 633*

W

- Wagener, Henry P., Rosenberg, E. F., and Keith, N. M., 126*
 Wald, Maurice H., Lindburg, H. A., and Barker, M. H., 763*
 Walter, R., 122*
 Wedd, A. M., and Blair, H. A., 536
 Wegria, R., Williams, J. R., Jr., and Harrison, T. R., 510*
 Weinstein, W., Katz, L. N., Friedman, M., and Rodbard, S., 334
 Weir, David R., 761*
 Weiss, Morris M., 103, 711
 Weiss, Soma, Kunkel, P., and Stead, E. A., Jr., 755*
 Weitzmann, G., 513*
 Westcott, F. H., and Wright, I. S., 761*
 Westphal, K., and Sievert, C., 509*
 Wheeler, Charles H., Stewart, H. J., Deitrick, J. E., and Crane, N. F., 127*
 White, Paul D., and Comeau, W. J., 158, 616
 —, Gordon, W. H., and Bland, E. F., 10
 —, Thompson, W. P., and Comeau, W. J., 286
 —, Wise, N. B., and Comeau, W. J., 701
 Whitehill, M. Richard, Longcope, W. T., and Williams, Russell, 758*
 Wilensky, Nathan D., and Collens, W. S., 624
 Will, Charles, Martin, W. C., and Tuohy, E. L., 728
 Williams, John R., Jr., and Grossman, E. B., 383*
 —, Wegria, R., and Harrison, T. R., 510*

Williams, Marvin M. D., Roth, G. M., and Sheard, C., 385*
 Williams, Russell, Whitehill, M. R., and Longcope, W. T., 758*
 Willius, Frederick A., and Baker, T. W., 382*
 —, and Boland, E. W., 512*
 —, and Dry, T. J., 138
 Wilson, C., and Pickering, G. W., 120*
 Winternitz, M., and Langendorf, R., 122*
 Wise, N. Bowman, Comeau, W. J., and White, P. D., 701
 Wolferth, Charles C., and Margolies, A., 639*
 Wolffe, Joseph B., Pescatore, J. A., and Digilio, V. A., 489
 Women, coronary thrombosis among, 382*
 Worth, Harold, Chen, K. K., and Robbins, E. B., 507*

Wosika, Paul H., Maher, C. C., Sanders, A., and Plice, S. G., 742
 Wright, Irving S., and Littauer, D., 325
 —, and Westcott, F. H., 761*

X

X-ray (*see* Roentgenogram)

Z

Zachrisson, C. G., Liljestrand, G., Lys-holm, E., and Nylin, G., 406
 Zazeela, Herman, Abramson, D. I., and Marrus, J., 194
 Zeus, L., 753*
 Zinn, C. J., Griffith, J. O., and Comroe, B. I., 633*
 Zurrow, Herman, Saland, G., and Klein, C., 581

